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PATENT APPLICATION



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, Surulichamy Senthil KUMAR, aged 31 years, son of V. Surulichamy, resident of 187, 3rd street, New Colony, Chengalpattu – 603 002 and citizen of India, hereby declare and state:

I. BACKGROUND

1. I have a Master's degree in Chemistry, which was conferred upon me by Bharathidhasan University in Tamilnadu, India, in 1995.
2. I have been employed by Orchid Chemicals and Pharmaceuticals Limited ("Orchid") since 1995 and I have a total of 8 years of work and research experience in cephalosporin synthesis technology.
3. I am familiar with the above-captioned patent application, including the present claims of that application, which appear in Exhibit 1.

4. I am not an inventor of the subject matter claimed in the above-captioned patent application.

II. FURACA SYNTHESIS AT ORCHID

5. Since before 1995, it has been known that preparation of cephalosporin can be split into two stages: (A) formation of an intermediate "furaca" (3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid), and (B) conversion of furaca to cephalosporin.

6. During my tenure at Orchid, a team of senior scientists employed by Orchid was set up to work on such processes under Dr. Gautam K. Das's leadership. Dr. Das (who worked with Mr. Bhausaheb P. Khandangale) and Mr. Pramod N. Deshpande were the core members of this team. I was one several assistant chemists that helped Mr. Deshpande and Dr. Das by performing experiments according to their instructions. The assistant chemists included, *inter alia*, Mr. Raja Jeya Kumar, Mr. Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220), Mr. Venkatachari Mukundan, Mr. S. Srinivasan and me. Mr. Uthira Kumar was employed by Orchid and worked in the laboratory during the course of all of the experiments described herein.

7. The laboratory in which Mr. Deshpande supervised the other assistant chemists and me was a small laboratory. Generally, no more than four to five assistant chemists worked in the laboratory at any one time. The other assistant chemists and I routinely discussed the experiments that we were carrying out in accordance with Mr. Deshpande's instructions. Such discussions were particularly common when the other assistant chemists and I were working on the same or related experiments.

8. Mr. Deshpande and Dr. Das were experienced chemists with substantial experience in the art of cephalosporin synthesis. Mr. Uthira Kumar was much less experienced in this area. In particular, Mr. Uthira Kumar was a recent college graduate with no practical experience when he was hired to assist with the project. Mr. Uthira Kumar had only one year of experience as a trainee chemist at Orchid and less than a year of experience as a probationary chemist at Orchid when the invention was conceived and first reduced to practice by and on behalf of the core members of the team as further detailed below.

9. On an almost daily basis, Mr. Deshpande met with the other assistant chemists and me to discuss Mr. Deshpande's and Dr. Das's ideas for improvement of processes for the production of cephalosporin. At Mr. Deshpande's meetings with the other assistant chemists and me, we reviewed the outcome of the previous day's work and Mr. Deshpande instructed us as to the next work to be performed. Mr. Deshpande provided the details of the experiments to be performed, including the chemicals to be used, the amounts and proportions thereof, and the manner in which they were to be reacted. The other assistant chemists and I performed most of the experiments, and reported the outcome of the experiments to Mr. Deshpande.

10. The other assistant chemists and I only performed experiments that were expressly requested by Mr. Deshpande and Dr. Das. All significant parameters of such experiments were established by Mr. Deshpande's instructions to the other assistant chemists and me.

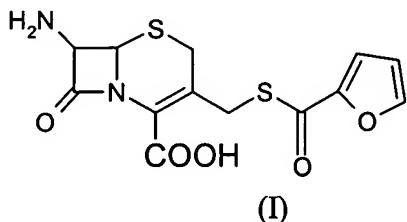
11. In accordance with Orchid's laboratory practices, the other assistant chemists and I recorded most of the experiments that we carried out on the project in a common laboratory notebook. In addition, various preliminary experiments were recorded in a separate notebook that Mr. Deshpande maintained. Entries in the common laboratory notebook were given titles identifying the object product and an experiment number, e.g., "FURACA #03," "FURACA

#04," "CEFTIOFUR #05." Entries in the separate notebook were given as titles alphanumeric experiment numbers indicating the chronological position of an experiment in a sequence of experiments. In particular, the separate notebook included entries having "N" titles, e.g., "FURACA/N/03," "FURACA/N/04," etc., describing furaca synthesis via a "new route." This new route involved the novel use of a catalyst solution of boron trifluoride in an organic solvent or in a mixture of organic solvents, as further reduced to practice in the "Furaca" experiments described below.

12. Mr. Uthira Kumar had access to the common laboratory notebook described in paragraph 11 above during the course of all of the experiments described herein, and periodically made entries in the common laboratory notebook, as reflected by his handwriting, which I recognize therein. For example, the common notebook describes an experiment entitled "FURACA #03" (Exhibit 8) described below, which was conducted by Mr. Uthira Kumar and is reported in the common notebook in his handwriting. Mr. Uthira Kumar had access to and made entries in the common laboratory notebook after making his entry describing "FURACA #03," and after entries describing the experiments "FURACA #04" (Exhibit 9), "Furaca #06" (Exhibit 10), "CEFTIOFUR #05" (Exhibit 11), and "FURACA #10" (Exhibit 12), all described below, were made by other assistant chemists. This access is evidenced by Mr. Uthira Kumar's entries into the common notebook in his handwriting describing the experiments entitled "PDL/ACF/048/98," "PDL/ACF/051/98," "PDL/ACF/053/98," "PDL/ACF/055/98," "PDL/ACF/056/98" and "PDL/ACF/048/98" (collectively Exhibit 13), each of which was made after the entries entitled "FURACA #04," "Furaca #06," "CEFTIOFUR #05" and "FURACA #10," and before November 27, 2000.

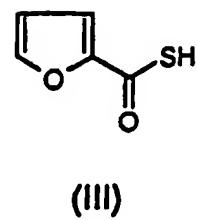
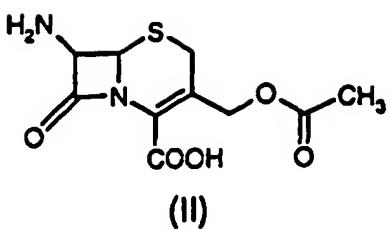
13. Mr. Uthira Kumar also had knowledge about the separate laboratory notebook described in paragraph 11. Mr. Uthira Kumar's knowledge about the separate laboratory notebook is also evidenced in Exhibit 8. In reporting the "FURACA #03" experiment, Mr. Uthira Kumar initially used the title "N-15." This illustrates, at the very least, Mr. Uthira Kumar's knowledge about the separate laboratory notebook described in paragraph 11.

14. Before November 27, 2000, at Mr. Deshpande's and Dr. Das's instruction, the other assistant chemists and I carried out experiments in which a cephalosporin compound (furaca: 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) represented by formula (I),



was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) of the formula (III) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA) of the formula (II), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.



15. In a series of meetings with the assistant chemists, which took place before November 27, 2000, Mr. Deshpande instructed the assistant chemists to prepare furaca by combining (i) boron trifluoride (BF_3) in ethyl acetate and acetic acid as a mixture of organic solvents with (ii) 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) in which the TFA was prepared and with (iii) 7-aminocephalosporanic acid (7-ACA), to precipitate the resultant furaca, and to determine the yield and purity of the resultant furaca.

16. In accordance with the instructions that Mr. Deshpande gave the other assistant chemists and me at those meetings, before November 27, 2000, three of the other assistant chemists and I had performed experiments involving the preparation of furaca that had been described by Mr. Deshpande at the meetings. Those other assistant chemists were Messrs. Raja Jeya Kumar, Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220) and Venkatachari Mukundan.

III. FURACA/N/06 EXPERIMENT

17. Exhibit 6 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/06," reflecting an experiment performed by me at Mr. Deshpande's direction before November 27, 2000.

18. I met with Mr. Deshpande and discussed the process described in the following paragraphs 20-21 prior to performance of the experiment "FURACA/N/06."

19. In Exhibit 6, the section entitled "FURACA/N/06" describes the preparation of furaca in a representative experiment carried out by me in accordance with the instructions given to me by Mr. Deshpande, in Mr. Deshpande's handwriting and entered into the notebook by Mr. Deshpande.

20. In the "FURACA/N/06" experiment in Exhibit 6, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

21. In particular, the section entitled "FURACA/N/06" in Exhibit 6 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 25.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") and 92 g of a mixture of boron trifluoride (BF_3) and acetic acid (abbreviated "Ac") were added to 75 ml of ethyl acetate -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 35°C;

b. 90 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/05") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 2 hours and 30 minutes at 40°C;

c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with sodium hydrogen sulfite (abbreviated "hydro");

d. the pH of the water/reaction mass mixture was then adjusted to 4.5 with ammonia (abbreviated "NH₃") solution at 20°C;

e. solid furaca was precipitated from the reaction mixture, and filtered. As reported in the section entitled "FURACA/N/06" in Exhibit 6, the dry weight of the resulting, furaca was 25.1 g, it had a moisture content (abbreviated "M/c") of 1.44% and the purity of the furaca was assayed and found to be 96.54%. The identity of the obtained furaca was confirmed by comparing with a working standard.

22. I met with Mr. Deshpande and discussed the results of the experiment "FURACA/N/06" following completion of that experiment before November 27, 2000.

23. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed me to carry out as described in paragraphs 20-21 above, and that Mr. Deshpande recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided me reflected in the separate notebook.

24. In particular, the instructions that Mr. Deshpande gave me that are reflected in the section entitled "FURACA/N/06" in Exhibit 6 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

IV. FURACA/N/07 EXPERIMENT

25. Exhibit 6 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/07," reflecting an experiment performed by me at Mr. Deshpande's direction before November 27, 2000.

26. I met with Mr. Deshpande and discussed the process described in the following paragraphs 28-29 prior to performance of the experiment "FURACA/N/07."

27. In Exhibit 6, the section entitled "FURACA/N/07" describes in the preparation of

furaca in a representative experiment carried out by me in accordance with the instructions given to me by Mr. Deshpande, in Mr. Deshpande's handwriting and entered into the notebook by Mr. Deshpande.

28. In the "FURACA/N/07" experiment in Exhibit 6, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

29. In particular, the section entitled "FURACA/N/07" in Exhibit 6 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 25.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") was combined with 185 ml of an ethyl acetate/boron trifluoride (BF_3) stock solution and 15 ml of acetic acid (abbreviated "Ac") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid;
- b. 90 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/05") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred

for 4 hours and 30 minutes at 40°C;

- c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with sodium hydrogen sulfite (abbreviated "hydro");
- d. the pH of the water/reaction mass mixture was then adjusted to 4.5 with ammonia (abbreviated "NH₃") solution at 20°C;
- e. solid furaca was precipitated from the reaction mixture, and filtered.

As reported in the section entitled "FURACA/N/07" in Exhibit 6, the dry weight of the resulting furaca was 24.8 g, it had a moisture content (abbreviated "M/c") of 2.0% and the purity of the furaca was assayed and found to be 97.48%. The identity of the obtained furaca was confirmed by comparing with a working standard.

30. I met with Mr. Deshpande and discussed the results of the experiment "FURACA/N/07" following completion of that experiment before November 27, 2000.

31. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed me to carry out as described in paragraphs 28-29 above, and that Mr. Deshpande recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided me reflected in the separate notebook.

32. In particular, the instructions that Mr. Deshpande gave me that are reflected in the section entitled "FURACA/N/07" in Exhibit 6 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of

organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

V. FURACA/N/12 EXPERIMENT

33. Exhibit 7 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/12," reflecting an experiment performed by me at Mr. Deshpande's direction before November 27, 2000.

34. I met with Mr. Deshpande and discussed the process described in the following paragraphs 36-37 prior to performance of the experiment "FURACA/N/12."

35. In Exhibit 7, the section entitled "FURACA/N/12" describes the preparation of furaca in a representative experiment carried out by me in accordance with the instructions given to me by Mr. Deshpande, in Mr. Deshpande's handwriting and entered into the notebook by Mr. Deshpande.

36. In the "FURACA/N/12" experiment in Exhibit 7, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

37. In particular, the section entitled "FURACA/N/12" in Exhibit 7 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 100.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were added to a mixture of 700 ml ethyl acetate, 60 ml acetic acid and 140 g boron trifluoride (BF_3) -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 25°C;
- b. 252 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/12") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 1 hour and 30 minutes at 40°C;
- c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with 2.0 g sodium hydrogen sulfite (abbreviated "hydro");

d. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 185 ml of ammonia (abbreviated "NH₃") solution at 25°C;

e. solid furaca was precipitated from the reaction mixture, and filtered and washed. As reported in section entitled "FURACA/N/12" in Exhibit 7, the dry weight of the resulting furaca was 116.3 g and the purity of the furaca was assayed and found to be 97.73%. The identity of the obtained furaca was confirmed by comparing with a working standard.

38. I met with Mr. Deshpande and discussed the results of the experiment "FURACA/N/12" following completion of that experiment before November 27, 2000.

39. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed me to carry out as described in paragraphs 36-37 above, and that Mr. Deshpande recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided me reflected in the separate notebook.

40. In particular, the instructions that Mr. Deshpande gave me that are reflected in the section entitled "FURACA/N/12" in Exhibit 7 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further

called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VI. FURACA #03 EXPERIMENT

41. Exhibit 8 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #03," reflecting an experiment performed by Mr. Uthira Kumar at Mr. Deshpande's direction before November 27, 2000.

42. Mr. Deshpande met with Mr. Uthira Kumar and discussed the process described in the following paragraphs 44-46 prior to performance of the experiment "FURACA #03." I was aware of Mr. Deshpande's meetings with Mr. Uthira Kumar to give him such instructions, and contemporaneously observed Mr. Uthira Kumar's entries in the common notebook relating to the process performed in the experiment "FURACA #03."

43. Exhibit 8 describes in two stages the preparation of furaca carried out by Mr. Uthira Kumar in accordance with the instructions given to him by Mr. Deshpande, in handwriting that I recognize as Mr. Uthira Kumar's handwriting and entered into the notebook by Mr. Uthira Kumar.

44. In the first stage, entitled "Preparation of TFA" in Exhibit 8, a solution of 2-

thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 8 describes Mr. Deshpande's instructions to Mr. Uthira Kumar, in accordance with which:

- a. 700 ml of demineralized water (abbreviated "DMW") and 75.0 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT"), the mixture was stirred to obtain a clear solution and the charging funnel was flushed with an additional 30 ml of demineralized water;
- b. 46.0 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol "'") at 20-25°C and then stirred for an additional 5 minutes;
- c. 500 ml of ethyl acetate (abbreviated "EtOAC") was then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 10-15 minutes;
- d. the resulting organic layer (abbreviated "OL₁") and aqueous layer were separated;
- e. an additional 350 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-25°C;
- f. the organic and aqueous layers were again separated; and 200 ml of ethyl acetate was added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by addition of 1:1 hydrochloric acid at 20-25°C;
- g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") containing the produced TFA was kept for the next stage.

45. In the second stage, entitled "Preparation of Furaca" in Exhibit 8, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid)

was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in the first stage, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

46. In particular, Exhibit 8 describes Mr. Deshpande's instructions to Mr. Uthira Kumar, in accordance with which:

a. 103.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into a mix of boron trifluoride (BF_3) catalyst-purged ethyl acetate (abbreviated "EtOAc")

and acetic acid (abbreviated "HOAc") -- i.e., 7-ACA was combined with a catalyst solution of

boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 20°C;

b. 260.0 ml of the TFA solution prepared in the first stage (i.e. a solution of 2-thiofuroic acid in the solvent ethyl acetate) were added to the resulting mixture;

c. the temperature was maintained at 30°C for two hours;

d. after completion of the reaction, the reaction mass was then transferred into 300.0 ml of demineralized water precooled to 15°C, along with 2.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");

e. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated " NH_3 ") solution at 20-25°C over 25-30 minutes;

f. the product was stirred for 30 minutes at 20-25°C; and
g. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate.

47. Mr. Deshpande met with Mr. Uthira Kumar and discussed the results of the experiment "FURACA #03" following completion of that experiment. I was aware of Mr. Deshpande's meetings with Mr. Uthira Kumar to follow up on such experiments, and observed Mr. Uthira Kumar's entries in the common notebook relating to the results obtained in the experiment "FURACA #03." I saw these entries in the common notebook within three days after they were made as I made my own entries in that notebook.

48. As all of the instructions for preparing furaca as described in the experiment "FURACA #03" were provided to Mr. Uthira Kumar by Mr. Deshpande, I believe that Mr. Uthira Kumar learned the process described in paragraphs 44-46 from Mr. Deshpande.

49. I have reviewed and understand claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 8). The subject matter of those claims appears in all significant respects to be the subject matter that Mr. Deshpande instructed Mr. Uthira Kumar to carry out as described in paragraphs 44-46 above, and that he recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided to Mr. Uthira Kumar and reflected in the common notebook.

50. In particular, the instructions that Mr. Deshpande gave Mr. Uthira Kumar that are reflected in Exhibit 8 specifically identified a process to prepare furaca. The instructions called

for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VII. FURACA #06 EXPERIMENT

51. Exhibit 10 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Furaca #06," reflecting an experiment performed by Mr. Mukundan and me at Mr. Deshpande's direction before November 27, 2000.

52. Mr. Deshpande met with Mr. Mukundan and me and discussed the process described in the following paragraphs 54-56 prior to and after performance of the experiment "Furaca #06."

53. Exhibit 10 accurately describes in two stages the preparation of furaca carried out by Mr. Mukundan and me in accordance with the instructions given to us by Mr. Deshpande, in Mr. Mukundan's and my respective handwritings and entered into the notebook by Mr.

Mukundan and me (Mr. Raja Jeya Kumar contemporaneously wrote in the "OL₃" entry on the second page of the "Furaca #06" report).

54. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 10, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;
- b. 27.5 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol "'") at 20-25°C and then the solution was stirred for an additional 5 minutes;
- c. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 15-20 minutes;
- d. the resulting organic and aqueous layers were separated, and the organic layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 10, in a Table headed "Reaction Monitoring," "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained 98.17% pure 2-thiofuroic acid.
- e. an additional 175 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated

"NaHCO₃") in 15-20 minutes, and the mixture was then stirred at 20-22°C over 30 minutes;

f. the organic and aqueous layers were again separated, 100 ml of ethyl acetate were added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by 1:1 hydrochloric acid;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the second page of Exhibit 10, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 96.5 % pure 2-thiofuroic acid;

h. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

55. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 10, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

56. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 200 ml of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container and the temperature was reduced to 0°C;
- b. the mixture was then purged with 68.5 g of boron trifluoride (BF_3) to form a catalyst solution of BF_3 in an organic solvent;
- c. 0.15 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") was then added to the container, and the mixture was stirred for 5 minutes;
- d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") followed by 130 ml of the 2-thiofuroic acid/ethyl acetate solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container with the catalyst solution of BF_3 in an organic solvent and the mixture was stirred until completion of the reaction at 30°C;
- e. separately, 150 ml of demineralized water were cooled to 15°C and 0.15 g of ethylenediaminetetraacetic acid were added to the water;
- f. the reaction mass was then transferred into the demineralized water followed by addition of 1.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");
- g. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated "NH₃") solution at 25-30°C over 40-45 minutes;
- h. the product was stirred for 30 minutes at 20-25°C; and
- i. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate. As reported in Exhibit 10, the wet weight of the resulting furaca was 116.8 g. The identity of the obtained furaca was confirmed by comparing with a working standard.

57. Mr. Deshpande met with Mr. Mukundan and me and discussed the results of the experiment "Furaca #06" following completion of that experiment before November 27, 2000.

58. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed us to carry out as described in paragraphs 54-56 above, and that we recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that were provided by Mr. Deshpande and reflected in the common notebook.

59. In particular, the instructions that Mr. Deshpande gave us that are reflected in Exhibit 10 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

60. Mr. Raja Jeya Kumar and I were both familiar with the results of the foregoing experiment "Furaca #06" (and we both took part in recording the procedures and results of the

experiment in the common laboratory notebook) in preparation for the following "CEFTIOFUR #05" experiment, in which the product of the "Furaca #06" experiment was used to prepare ceftiofur before November 27, 2000.

VIII. CEFTIOFUR #05 EXPERIMENT

61. Exhibit 11 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Ceftiofur #05," reflecting an experiment performed by Mr. Raja Jeya Kumar and me at Mr. Deshpande's direction before November 27, 2000. Mr. Deshpande gave the instructions to Mr. Raja Jeya Kumar and me to carry out this experiment.

62. Exhibit 11 describes the preparation of ceftiofur carried out by Mr. Raja Jeya Kumar and me in accordance with the instructions given to us by Mr. Deshpande, in Mr. Raja Jeya Kumar's and my handwriting and entered into the notebook by Mr. Raja Jeya Kumar and me.

63. In the experiment described in Exhibit 11, ceftiofur was synthesized using furaca that was obtained in the previous experiment entitled "Furaca #06" described in paragraphs 51-60 above. The experiment described in Exhibit 11 confirms that the furaca made in the experiment "Furaca #06" was useful in the manufacture of ceftiofur.

64. In particular, Exhibit 11 correctly describes that, in accordance with Mr. Deshpande's instructions:

a. 443.2 ml of demineralized water (abbreviated "DMW") and 500 g of tetrahydrofuran (abbreviated "THF") were charged into a container and the temperature was

reduced to 5°C;

b. 116.8 g of the furaca (abbreviating "(3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid)") obtained from "Furaca #06" experiment followed by 74.0 g of methoxyiminothiazole intermediate (abbreviated "MAEM") were charged into the container at 3-5°C;

c. 40 ml of triethylamine (abbreviated "TEA") were added over 3 hours at 3-5°C and the temperature was maintained until completion of the reaction;

d. 750 ml of ethyl acetate (abbreviated "EtOAc") and 1.0 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") were charged into the container at 15°C over 15 minutes, and the layers were separated;

e. the aqueous layer was extracted with 400 ml of ethyl acetate for 15 minutes and the layers were again separated;

f. the organic layer was extracted with 200 ml of demineralized water and the layers were again separated, and the aqueous layer was combined with the rich aqueous layer from step e;

g. 135.0 g of sodium chloride (abbreviated "NaCl") and 950 ml of tetrahydrofuran were added to the solution at 18-20°C;

h. the pH of the solution was adjusted to 3.0-3.1 with concentrated hydrochloric acid (abbreviated "conc. HCl") at 18-20°C over 20-25 minutes, the layers were then separated and the aqueous phase was discarded;

i. the organic phase was charcoalized at 18-20°C over 40 minutes;

j. the solution was filtered and the bed was washed with 100 ml of tetrahydrofuran;

- k. the pH was adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C over 10-15 minutes;
- l. the solution was seeded with 1.0 g of ceftiofur hydrochloride (abbreviated "CFUR HCl") and stirred at 18-20°C over 1 hour;
- m. the pH was again adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C;
- n. the solution was again seeded with 1.0 g of ceftiofur hydrochloride and stirred at 18-20°C over 1 hour;
- o. 450 ml of iso-propyl ether (abbreviated "IPE") were added to the solution at 18-20°C over 40 minutes;
- p. the solution was stirred at 18-20°C over 1 hour and then filtered;
- q. the filtrate was washed with 250 ml of isopropyl ether and dried, and 87.4 g of dry ceftiofur were obtained and purity of ceftiofur prepared by this process was assayed by HPLC and found to be 97.45%. The identity of the obtained ceftiofur was confirmed by comparing with a working standard.

IX. FURACA #10 EXPERIMENT

65. Exhibit 12 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #10," reflecting an experiment performed by me at Mr. Deshpande's direction before November 27, 2000. Mr. Deshpande gave the instructions to me to carry out this experiment.

66. Mr. Deshpande met with me and discussed the process described in the following

paragraphs 68-70 prior to performance of the experiment "FURACA #10."

67. Exhibit 12 describes in two stages the preparation of furaca carried out by me in accordance with the instructions given to me by Mr. Deshpande, in my handwriting and entered into the notebook by me.

68. In the first stage, entitled "Stage I: Preparation of TFA" in Exhibit 12, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 12 correctly describes that, as Mr. Deshpande had instructed:

- a. 365 ml of demineralized water (abbreviated "DMW") were charged into a container and the temperature was reduced to 20-25°C;
- b. 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into the container and the mixture was stirred for 5 minutes (minutes being abbreviated with the symbol "'") to obtain a clear solution;
- c. 27.5 g of 2-furoyl chloride were added over 40-45 minutes at 20-25°C and then stirred while maintaining temperature for 10 minutes;
- d. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 22-25°C over 15 minutes;
- e. the resulting organic and aqueous layers were separated, and the aqueous layer was discarded; the organic layer (abbreviated "OL₁") was subjected to high performance liquid chromatography; as reported in the Table on the first page of Exhibit 12, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained 97.34 % pure 2-thiofuroic acid;
- f. an additional 175 ml of demineralized water were then added to the

organic layer, and the pH was adjusted to 7.0 to 7.1 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-22°C over 15 minutes;

g. the mixture was then stirred at 20-22°C over 30 minutes, and then the organic and aqueous layers were again separated;

h. 100 ml of ethyl acetate were added to the aqueous layer and the pH was adjusted to 0.9-1.0 by adding 1:1 hydrochloric acid at 20-22°C over 15 minutes;

i. the mixture was stirred at 20-22°C over 15 minutes, and then the organic and aqueous layers were again separated;

j. the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the first page of Exhibit 12, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 97.48 % pure 2-thiofuroic acid;

k. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

69. In the second stage, entitled "STAGE II: FURACA PREPARATION" in Exhibit 12, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

70. In particular, Exhibit 12 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 200 g of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container at room temperature (abbreviated "RT") and the temperature was reduced to 0°C;
- b. the mixture was then purged with 68.5 g of boron trifluoride (BF_3) gas at less than 10°C;
- c. 0.3 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") were then added to the container, and the mixture was stirred for 5 minutes at 15°C;
- d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into the container with the catalyst solution of boron trifluoride and organic solvents and stirred for 5 minutes, and then 130 ml of the 2-thiofuroic acid solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container (i.e., combined with the other components) and the mixture was stirred until for 2.5 hours at 30°C, the resulting reaction mass was divided equally into two parts;
- e. the first part of the reaction mass was charged into 75.0 ml of demineralized water precooled to 15°C, 0.15 g of ethylenediaminetetraacetic acid and 0.5 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") were then added;
- f. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 18-20% ammonia (abbreviated "NH₃") solution at 25-30°C over 40-45 minutes;
- g. the mixture was stirred for 30 minutes at 25°C and then filtered;

- h. the filtrate was washed by spray, slurry and spray with demineralized water;
- i. the wet reaction mass was transferred to a round bottom flask (abbreviated "RBF"), 75 ml of ethyl acetate were added, the mixture was stirred for 15 minutes at 25°C and then filtered;
- j. the filtrate was washed by spray with 25 ml of ethyl acetate;
- k. the product was dried for 2-3 hours at 30-35°C and analyzed, 28.4 g of dry furaca were obtained with quantitative purity of 91.93, the identity of the obtained furaca was confirmed by comparing with a working standard;
- l. the second part of the reaction mass was charged into 75.0 ml of demineralized water precooled to 15°C, 0.15 g of ethylenediaminetetraacetic acid and 0.5 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") were then added;
- m. the pH of the water/reaction mass mixture was then adjusted to 3.0 with 18-20% ammonia (abbreviated " NH_3 ") solution at 25-30°C over 40-45 minutes;
- n. the mixture was stirred for 30 minutes at 25°C and then filtered;
- o. the filtrate was washed by spray, slurry and spray with demineralized water;
- p. the wet reaction mass was transferred to a round bottom flask (abbreviated "RBF"), 75 ml of ethyl acetate were added, the mixture was stirred for 15 minutes at 25°C and then filtered;
- q. the filtrate was washed by spray with 25 ml of ethyl acetate;

r. the product was dried for 2-3 hours at 30-35°C and analyzed, 29.5 g of dry furaca were obtained with quantitative purity of 81.84. The identity of the obtained furaca was confirmed by comparing with a working standard.

71. Mr. Deshpande met with me and discussed the results of the experiment "FURACA #10" following completion of that experiment before November 27, 2000.

72. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed me to carry out as described in paragraphs 68-70 above, and that I recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that were provided to me by Mr. Deshpande and reflected in the common notebook.

73. In particular, the instructions that Mr. Deshpande gave me that are reflected in Exhibit 12 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of

alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

X. CONCLUSION

74. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 12.08.2003.


Surulichamy Senthil Kumar

Attachments:

- | | |
|------------|--|
| Exhibit 1 | - Claims |
| Exhibit 3 | - U.S. Patent No. 6,476,220 B2 |
| Exhibit 6 | - Page from Separate Laboratory Notebook |
| Exhibit 7 | - Page from Separate Laboratory Notebook |
| Exhibit 8 | - Pages from Common Laboratory Notebook |
| Exhibit 10 | - Pages from Common Laboratory Notebook |
| Exhibit 11 | - Pages from Common Laboratory Notebook |
| Exhibit 12 | - Pages from Common Laboratory Notebook |
| Exhibit 13 | - Pages from Common Laboratory Notebook |

PATENT APPLICATION



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

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AUG 18 2003
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RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, Vivekshit R NAIDU, aged 32 years, son of Rammurthy J Naidu, resident of No. 1, Padmavathi Avenue, Thirumalai Nagar Annexue, Perungudi, Chennai 600 096, Tamilnadu and citizen of India, hereby declare and state:

1. I have been employed by Orchid Chemicals and Pharmaceuticals Limited ("Orchid") since 1997.
2. My present job title is Executive. I work in the personnel Department at Orchid. In performing my job at Orchid, I routinely view and work with the personnel files of other Orchid employees.
3. I have studied and am familiar with the personnel files of Mr. Uthira Kumar. The personnel files of Mr. Uthira Kumar were created at or near the time that the information contained therein was transmitted to Orchid and, further, those files were kept and created in the ordinary course of Orchid's business.

4. I am aware of the time period during which the invention described in the above-captioned patent application is alleged to have been conceived and first reduced to practice by Dr. Gautam Das, Mr. Bhausaheb P. Khadangale and Dr. Pramod N. Deshpande.

5. Mr. Uthira Kumar was a recent college graduate with no practical experience when he was hired to work at Orchid. Mr. Uthira Kumar had only one year of experience as a trainee chemist at Orchid and less than a year of experience as a probationary chemist at Orchid when the invention is alleged to have been conceived and first reduced to practice by Dr. Das, Mr. Khadangale and Dr. Deshpande. See Exhibit 4, which is a copy of Mr. Uthira Kumar's resume showing no prior employment at the time of his hiring by Orchid, and Exhibit 5, which is a copy of the offer letter to Mr. Uthira Kumar describing in sections 1 and 2 the training and probationary periods of Mr. Kumar's employment by Orchid. Exhibits 4 and 5 are both signed by Mr. Uthira Kumar, and are both contemporaneously created business records kept in the ordinary course of business by Orchid.

6. I am not an inventor of the subject matter claimed in the above-captioned patent application.

7. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 12-08-2003

Vivek
VIVEKSHIT R NAIDU

Attachments:

- Exhibit 4 - Uthira Kumar Resume
- Exhibit 5 - Uthira Kumar Offer Letter



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AUG 16 2003

PATENT APPLICATION

TECH CENTER 1600/2900

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, K.C. Pathak, aged 39 years, son of Bangali Bhushan, resident of Flat No. FF/A, Block-B, Sri Jayendra Colony, 4/360 I.T. High Road, Chennai-600 096 and citizen of India, hereby declare and state:

I. BACKGROUND

1. I have a Master's degree in (M. Sc.) in Organic Chemistry, which was conferred upon me by Agra University, Agra in 1983. Additionally I have M. Phil (Chemistry) conferred by Punjab University, Chandigarh, LL.B (Business, Labour, Tax and IPR Laws) from university of Delhi and Advanced Diploma in Management (Operations)

2. I have been employed by Orchid Chemicals and Pharmaceuticals Limited since May 1993 and I have a total of twenty years of work and research experience in Production, Process Development, Production Planning and Inventory Control.

3. I am familiar with the above-captioned patent application, including the present claims of that application, which appear in Exhibit 1.

4. I am not an inventor of the subject matter claimed in the above-captioned patent application.

II. ORCHID PHARMACEUTICALS AND CHEMICALS LIMITED

5. Orchid Pharmaceuticals and Chemicals Limited ("Orchid"), the assignee of the above-captioned patent application (see Exhibit 2, which is an assignment of the invention and application to Orchid), was founded in 1994 in India (which has been a WTO country since 1995). In that year, Orchid set up a Research and Development unit equipped with state-of-the art facilities to undertake and conduct research on pharmaceuticals on a laboratory scale, a pilot scale and for commercial viability, including a state-of-the art and highly reliable reagent, chemicals and equipment supply department in which high quality reagents, chemicals and equipment were kept available for use in Orchid's day-to-day work. Since at least 1995, Orchid has been vigorously implementing research projects on cephalosporin antibiotics such as Cephalexin, Cefpodoxime, Cefdinir, Cefadroxil and Ceftiofur.

6. The Orchid Research and Development unit has been given the ISO 2002 Certification for maintaining excellent manufacturing and quality systems.

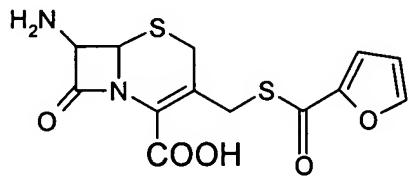
7. As part of its intensive and successful efforts to produce cephalosporin antibiotics, Orchid has engaged in development of innovative processes whereby cephalosporins can be manufactured economically on a commercial scale.

III. FURACA SYNTHESIS AT ORCHID

8. Since before 1995, it has been known that preparation of cephalosporin can be split into two stages: (A) formation of an intermediate "furaca" (3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid), and (B) conversion of furaca to cephalosporin.

9. During my tenure at Orchid, a team of senior scientists employed by Orchid was set up to work on such processes under the leadership of Dr. Gautam Das. Dr. Das (who worked with Mr. Bhausaheb P. Khadangale) and Mr. Pramod N. Deshpande (Dr. Das, Mr. Khadangale and Mr. Deshpande are the three named inventors on the above-captioned patent application) were the core members of this team.

10. Before November 27, 2000, Dr. Das, Mr. Khadangale and Mr. Deshpande conceived of the invention described in the present claims of the above-captioned patent application, and they carried out experiments and/or instructed assistant chemists to carry out experiments in which a cephalosporin compound (furaca: 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) represented by formula (I),



(I)

was prepared by a process comprising:

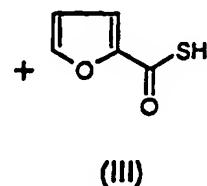
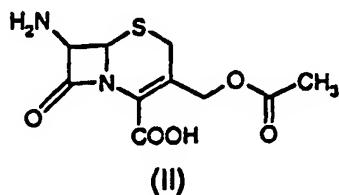
- (a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

(ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) of the formula (III) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA) of the formula (II), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.



11. After completion of experimentation to achieve the invention described above, but still before November 27, 2000, commercial feasibility of the process detailed in paragraph 10 above was tested by repeating all of the experimentation at the pilot plant and the plant for large-scale studies, before November 27, 2000. The process passed all tests, and proved to be economical.

IV. BATCH PROCESSING EXPERIMENTS

12. Exhibit 14 is a Batch Processing Record for a large scale performance of the process described in paragraph 10 above, as well as large scale preparation of ceftiofur from the product of that process, also dated before November 27, 2000, signed by Mr. Deshpande and me. The processes described in Exhibit 14 were carried out under my supervision (then Head of Production for Orchid) and under the supervision of Mr. Deshpande (then Head of the Orchid

Process Development Laboratory and one of the inventors of the above-captioned patent application). The work described in Exhibit 14 was carried out in the presence and under the direct supervision of Dr. Ashwani Kumar, who signed it as Shift Supervisor, by the individuals who initialed in the column "Sign of Shift Chemist/Operator" for each step of the process.

13. Exhibit 14 correctly describes, in its first phase, the details of an actual large scale production of furaca by combining (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent (ethyl acetate), (ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent ethyl acetate, and (iii) 7-aminocephalosporanic acid (7-ACA), and allowing them to react, and precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid, according to the process developed by Dr. Das, Mr. Khadangale and me.

14. In particular, steps 1-20 of the procedure outlined on the first two pages of the portion of Exhibit 14 entitled "Batch Processing - Furaca Preparation" describe the preparation of 2-thiofuroic acid (TFA) as a reactant for the ensuing process of producing furaca. As described in Exhibit 14, water, sodium sulfide, furoyl chloride and ethyl acetate were combined (see steps 1-8) and stirred and allowed to settle into organic and aqueous layers (see steps 9-12). After several separation steps (see steps 13-28), the product TFA in ethyl acetate (an organic solvent) was collected (see step 29 and step 38).

15. Then a solution of boron trifluoride (BF_3) in ethyl acetate (an organic solvent) was prepared (see steps 31-36), and combined with 7-ACA and the previously prepared TFA-in-a-solvent (see steps 37-38), and the mixture was allowed to react at about 30°C (see steps 39-40). The reaction was monitored by high performance liquid chromatography ("HPLC"), particularly with respect to the produced furaca (abbreviated "ACF") and the reactants 7-ACA and TFA, and the reaction monitoring data was recorded on page 3 of Exhibit 14. Thereafter, solid furaca

(ACF) was precipitated and recovered as a mill cake (see steps 41-62). The product furaca was thereafter washed (see steps 1-20 on page 6 of the portion of Exhibit 14 entitled "Batch Processing - Furaca Preparation"). The obtained furaca was assayed by HPLC and confirmed by comparing with a working standard.

16. Exhibit 14 also correctly describes, in its second and third phases, the further processing of the furaca product obtained in the first phase of batch processing and actual large scale production of ceftiofur using that furaca product. The preparation of ceftiofur using the obtained furaca confirms the usefulness of the furaca as an intermediate in the manufacture of ceftiofur.

17. The portion of Exhibit 14 entitled "Batch Processing Record - Extraction of Fluorides from ML" describes the further processing of the furaca product obtained in the first phase by extraction of fluorides. The portion of Exhibit 14 entitled "Batch Processing Record - Ceftiofur Hydrochloride" describes the manufacture of ceftiofur using that furaca product. The obtained ceftiofur product was assayed by HPLC and its identity was confirmed by comparing with a working standard.

18. This process was ultimately put into commercial production at Orchid.

V. CONCLUSION

19. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Application No. 10/035,178

Date: 11.08.2003

Kailash Chandra Pathak
Kailash Chandra Pathak

Attachments:

- Exhibit 1 - Claims
- Exhibit 2 - Assignment
- Exhibit 14 - Batch Processing Record



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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, VENKATACHARI Mukundan, aged 29 years, son of Venkatachari, resident of Old No. 33, New No. 81, Flat 14, Rams, 4th Main Road, Gandhi Nagar, Chennai, Tamilnadu, and citizen of India, hereby declare and state:

I. BACKGROUND

1. I have a Bachelor's degree in Chemical Technology which was conferred upon me by University of Bombay Department of Chemical Technology (UDCT), in Bombay in 1997.
2. I was employed by Orchid Chemicals and Pharmaceuticals Limited ("Orchid") from 1997 until 2000 and I have had a total of 6 years of work and research experience in cephalosporin synthesis technology.
3. I am familiar with the above-captioned patent application, including the present claims of that application, which appear in Exhibit 1.

4. I am not an inventor of the subject matter claimed in the above-captioned patent application.

II. FURACA SYNTHESIS AT ORCHID

5. Since before 1995, it has been known that preparation of cephalosporin can be split into two stages: (A) formation of an intermediate "furaca" (3-[2-furylcarbonyl]thiomethyl)-3-cephem-4-carboxylic acid), and (B) conversion of furaca to cephalosporin.

6. During my tenure at Orchid, a team of senior scientists employed by Orchid was set up to work on such processes under Dr. Gautam K. Das's leadership. Dr. Das (who worked with Mr. Bhausaheb P. Khandangale) and Mr. Pramod B. Deshpande were the core members of this team. I was one several assistant chemists that helped Mr. Deshpande and Dr. Das by performing experiments according to their instructions. The assistant chemists included, *inter alia*, Mr. Senthil Kumar, Mr. Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220), Mr. Raja Jeya Kumar, Mr. S. Srinivasan and me. Mr. Uthira Kumar was employed by Orchid and worked in the laboratory during the course of all of the experiments described herein.

7. The laboratory in which Mr. Deshpande supervised the other assistant chemists and me was a small laboratory. Generally, no more than four to five assistant chemists worked in the laboratory at any one time. The other assistant chemists and I routinely discussed the experiments that we were carrying out in accordance with Mr. Deshpande's instructions. Such discussions were particularly common when the other assistant chemists and I were working on the same or related experiments.

8. Mr. Deshpande and Dr. Das were experienced chemists with substantial experience in the art of cephalosporin synthesis. Mr. Uthira Kumar was much less experienced in this area. In particular, Mr. Uthira Kumar was a recent college graduate with no practical experience when he was hired to assist with the project. Mr. Uthira Kumar had only one year of experience as a trainee chemist at Orchid and less than a year of experience as a probationary chemist at Orchid when the invention was conceived and first reduced to practice by and on behalf of the core members of the team as further detailed below.

9. On an almost daily basis, Mr. Deshpande met with the other assistant chemists and me to discuss Mr. Deshpande's and Dr. Das's ideas for improvement of processes for the production of cephalosporin. At Mr. Deshpande's meetings with the other assistant chemists and me, we reviewed the outcome of the previous day's work and Mr. Deshpande instructed us as to the next work to be performed. Mr. Deshpande provided the details of the experiments to be performed, including the chemicals to be used, the amounts and proportions thereof, and the manner in which they were to be reacted. The other assistant chemists and I performed the experiments, and reported the outcome of the experiments to Mr. Deshpande.

10. The other assistant chemists and I only performed experiments that were expressly requested by Mr. Deshpande and Dr. Das. All significant parameters of such experiments were established by Mr. Deshpande's instructions to the other assistant chemists and me.

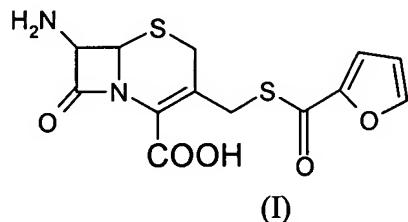
11. In accordance with Orchid's laboratory practices, the other assistant chemists and I recorded most of the experiments that we carried out on the project in a common laboratory notebook. In addition, various preliminary experiments were recorded in a separate notebook that Mr. Deshpande maintained. Entries in the common laboratory notebook were given titles identifying the object product and an experiment number, e.g., "FURACA #03," "FURACA

#04," "CEFTIOFUR #05." Entries in the separate notebook were given as titles alphanumeric experiment numbers indicating the chronological position of an experiment in a sequence of experiments. In particular, the separate notebook included entries having "N" titles, e.g., "FURACA/N/03," "FURACA/N/04," etc., describing furaca synthesis via a "new route." This new route involved the novel use of a catalyst solution of boron trifluoride in an organic solvent or in a mixture of organic solvents, as further reduced to practice in the "Furaca" experiments described below.

12. Mr. Uthira Kumar had access to the common laboratory notebook described in paragraph 11 above during the course of all of the experiments described herein, and periodically made entries in the common laboratory notebook, as reflected by his handwriting, which I recognize therein. For example, the common notebook describes an experiment entitled "FURACA #03" (Exhibit 8) described below, which was conducted by Mr. Uthira Kumar and is reported in the common notebook in his handwriting. Mr. Uthira Kumar had access to and made entries in the common laboratory notebook after making his entry describing "FURACA #03," and after entries describing the experiments "FURACA #04" (Exhibit 9), "Furaca #06" (Exhibit 10), "CEFTIOFUR #05" (Exhibit 11), and "FURACA #10" (Exhibit 12), all described below, were made by other assistant chemists. This access is evidenced by Mr. Uthira Kumar's entries into the common notebook in his handwriting describing the experiments entitled "PDL/ACF/048/98," "PDL/ACF/051/98," "PDL/ACF/053/98," "PDL/ACF/055/98," "PDL/ACF/056/98" and "PDL/ACF/048/98" (collectively Exhibit 13), each of which was made after the entries entitled "FURACA #04," "Furaca #06," "CEFTIOFUR #05" and "FURACA #10," and before November 27, 2000.

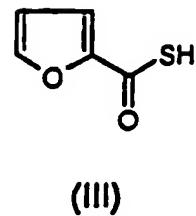
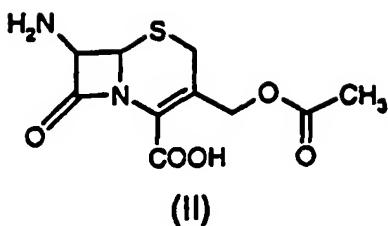
13. Mr. Uthira Kumar also had knowledge about the separate laboratory notebook described in paragraph 11. Mr. Uthira Kumar's knowledge about the separate laboratory notebook is also evidenced in Exhibit 8. In reporting the "FURACA #03" experiment, Mr. Uthira Kumar initially used the title "N-15." This illustrates, at the very least, Mr. Uthira Kumar's knowledge about the separate laboratory notebook described in paragraph 11.

14. Before November 27, 2000, at Mr. Deshpande's and Dr. Das's instruction, the other assistant chemists and I carried out experiments in which a cephalosporin compound (furaca: 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) represented by formula (I),



was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) of the formula (III) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA) of the formula (II), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.



15. In a series of meetings with the assistant chemists, which took place before November 27, 2000, Mr. Deshpande instructed the assistant chemists to prepare furaca by combining (i) boron trifluoride (BF_3) in ethyl acetate and acetic acid as a mixture of organic solvents with (ii) 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) in which the TFA was prepared and with (iii) 7-aminocephalosporanic acid (7-ACA), to precipitate the resultant furaca, and to determine the yield and purity of the resultant furaca.

16. In accordance with the instructions that Mr. Deshpande gave the other assistant chemists and me at those meetings, before November 27, 2000, three of the other assistant chemists and I had performed experiments involving the preparation of furaca that had been described by Mr. Deshpande at the meetings. Those other assistant chemists were Messrs. Senthil Kumar, Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220) and Raja Jeya Kumar.

III. FURACA #06 EXPERIMENT

17. Exhibit 10 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Furaca #06," reflecting an experiment performed by Messrs. Senthil Kumar and me at Mr. Deshpande's direction before November 27,

2000. Mr. Deshpande provided the instructions to us to carry out this experiment.

18. Mr. Deshpande met with Messrs. Senthil Kumar and me and discussed the process described in the following paragraphs 20-22 prior to and after performance of the experiment "Furaca #06."

19. Exhibit 10 accurately describes in two stages the preparation of furaca carried out by Messrs. Senthil Kumar and me in accordance with the instructions given to us by Mr. Deshpande, in Messrs. Senthil Kumar's and my respective handwritings and entered into the notebook by Messrs. Senthil Kumar and me (Mr. Jeya Kumar contemporaneously wrote in the "OL₃" entry on the second page of the "Furaca #06" report).

20. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 10, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;

b. 27.5 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol " ' ") at 20-25°C and then the solution was stirred for an additional 5 minutes;

c. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 15-20 minutes;

d. the resulting organic and aqueous layers were separated, and the organic

layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 10, in a Table headed "Reaction Monitoring," "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained 98.17% pure 2-thiofuroic acid.

e. an additional 175 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") in 15-20 minutes, and the mixture was then stirred at 20-22°C over 30 minutes;

f. the organic and aqueous layers were again separated, 100 ml of ethyl acetate were added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by 1:1 hydrochloric acid;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the second page of Exhibit 10, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 96.5 % pure 2-thiofuroic acid;

h. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

21. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 10, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

22. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 200 ml of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container and the temperature was reduced to 0°C;
- b. the mixture was then purged with 68.5 g of boron trifluoride (BF_3) to form a catalyst solution of BF_3 in an organic solvent;
- c. 0.15 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") was then added to the container, and the mixture was stirred for 5 minutes;
- d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") followed by 130 ml of the 2-thiofuroic acid/ethyl acetate solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container with the catalyst solution of BF_3 in an organic solvent and the mixture was stirred until completion of the reaction at 30°C;
- e. separately, 150 ml of demineralized water were cooled to 15°C and 0.15 g of ethylenediaminetetraacetic acid were added to the water;
- f. the reaction mass was then transferred into the demineralized water followed by addition of 1.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");
- g. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated " NH_3 ") solution at 25-30°C over 40-45 minutes;

h. the product was stirred for 30 minutes at 20-25°C; and
i. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate. As reported in Exhibit 10, the wet weight of the resulting furaca was 116.8 g. The identity of the obtained furaca was confirmed by comparing with a working standard.

23. Mr. Deshpande met with Mr. Senthil Kumar and me and discussed the results of the experiment "Furaca #06" following completion of that experiment before November 27, 2000.

24. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed us to carry out as described in paragraphs 20-22 above, and that we recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that were provided by Mr. Deshpande and reflected in the common notebook.

25. In particular, the instructions that Mr. Deshpande gave us that are reflected in Exhibit 10 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step

at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

26. Mr. Senthil Kumar and I were both familiar with the results of the foregoing experiment "Furaca #06" (and we both took part in recording the procedures and results of the experiment in the common laboratory notebook) in preparation for the following "CEFTIOFUR #05" experiment, in which the product of the "Furaca #06" experiment was used to prepare ceftiofur before November 27, 2000.

IV. CONCLUSION

27. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date:

14 - 8 - 2002



Venkatachari Mukundan

Attachments:

- Exhibit 1 - Claims
- Exhibit 3 - U.S. Patent No. 6,476,220 B2
- Exhibit 8 - Pages from Common Laboratory Notebook
- Exhibit 9 - Pages from Common Laboratory Notebook
- Exhibit 10 - Pages from Common Laboratory Notebook
- Exhibit 11 - Pages from Common Laboratory Notebook
- Exhibit 12 - Pages from Common Laboratory Notebook
- Exhibit 13 - Pages from Common Laboratory Notebook

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PATENT APPLICATION



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, Raja Jeya KUMAR, aged 32 years, son of P.John Muthiah resident of 34, III Main road, Anna nagar, Chengalpattu--603001 and citizen of India, hereby declare and state:

I. BACKGROUND

1. I have a degree in Chemistry, which was conferred upon me by Gandhigram Rural Institute in Tamilnadu, India, in 1993.
2. I have been employed by Orchid Chemicals and Pharmaceuticals Limited ("Orchid") since 1993 and I have a total of 9 years of work and research experience in cephalosporin synthesis technology.
3. I am familiar with the above-captioned patent application, including the present claims of that application, which appear in Exhibit 1.

4. I am not an inventor of the subject matter claimed in the above-captioned patent application.

II. FURACA SYNTHESIS AT ORCHID

5. Since before 1995, it has been known that preparation of cephalosporin can be split into two stages: (A) formation of an intermediate "furaca" (3-[2-furylcarbonyl]thiomethyl)-3-cephem-4-carboxylic acid), and (B) conversion of furaca to cephalosporin.

6. During my tenure at Orchid, a team of senior scientists employed by Orchid was set up to work on such processes under Dr. Gautam K. Das's leadership. Dr. Das (who worked with Mr. Bhausaheb P. Khandangale) and Mr. Pramod B. Deshpande were the core members of this team. I was one several assistant chemists that helped Mr. Deshpande and Dr. Das by performing experiments according to their instructions. The assistant chemists included, *inter alia*, Mr. Senthil Kumar, Mr. Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220), Mr. Venkatachari Mukundan, Mr. S. Srinivasan and me. Mr. Uthira Kumar was employed by Orchid and worked in the laboratory during the course of all of the experiments described herein.

7. The laboratory in which Mr. Deshpande supervised the other assistant chemists and me was a small laboratory. Generally, no more than four to five assistant chemists worked in the laboratory at any one time. The other assistant chemists and I routinely discussed the experiments that we were carrying out in accordance with Mr. Deshpande's instructions. Such discussions were particularly common when the other assistant chemists and I were working on the same or related experiments.

8. Mr. Deshpande and Dr. Das were experienced chemists with substantial experience in the art of cephalosporin synthesis. Mr. Uthira Kumar was much less experienced in this area. In particular, Mr. Uthira Kumar was a recent college graduate with no practical experience when he was hired to assist with the project. Mr. Uthira Kumar had only one year of experience as a trainee chemist at Orchid and less than a year of experience as a probationary chemist at Orchid when the invention was conceived and first reduced to practice by and on behalf of the core members of the team as further detailed below.

9. On an almost daily basis, Mr. Deshpande met with the other assistant chemists and me to discuss Mr. Deshpande's and Dr. Das's ideas for improvement of processes for the production of cephalosporin. At Mr. Deshpande's meetings with the other assistant chemists and me, we reviewed the outcome of the previous day's work and Mr. Deshpande instructed us as to the next work to be performed. Mr. Deshpande provided the details of the experiments to be performed, including the chemicals to be used, the amounts and proportions thereof, and the manner in which they were to be reacted. The other assistant chemists and I performed most of the experiments, and reported the outcome of the experiments to Mr. Deshpande.

10. The other assistant chemists and I only performed experiments that were expressly requested by Mr. Deshpande and Dr. Das. All significant parameters of such experiments were established by Mr. Deshpande's instructions to the other assistant chemists and me.

11. In accordance with Orchid's laboratory practices, the other assistant chemists and I recorded most of the experiments that we carried out on the project in a common laboratory notebook. In addition, various preliminary experiments were recorded in a separate notebook that Mr. Deshpande maintained. Entries in the common laboratory notebook were given titles

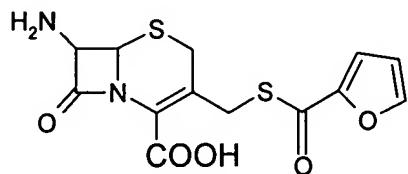
identifying the object product and an experiment number, e.g., "FURACA #03," "FURACA #04," "CEFTIOFUR #05." Entries in the separate notebook were given as titles alphanumeric experiment numbers indicating the chronological position of an experiment in a sequence of experiments. In particular, the separate notebook included entries having "N" titles, e.g., "FURACA/N/03," "FURACA/N/04," etc., describing furaca synthesis via a "new route." This new route involved the novel use of a catalyst solution of boron trifluoride in an organic solvent or in a mixture of organic solvents, as further reduced to practice in the "Furaca" experiments described below.

12. Mr. Uthira Kumar had access to the common laboratory notebook described in paragraph 11 above during the course of all of the experiments described herein, and periodically made entries in the common laboratory notebook, as reflected by his handwriting, which I recognize therein. For example, the common notebook describes an experiment entitled "FURACA #03" (Exhibit 8) described below, which was conducted by Mr. Uthira Kumar and is reported in the common notebook in his handwriting. Mr. Uthira Kumar had access to and made entries in the common laboratory notebook after making his entry describing "FURACA #03," and after entries describing the experiments "FURACA #04" (Exhibit 9), "Furaca #06" (Exhibit 10), "CEFTIOFUR #05" (Exhibit 11), and "FURACA #10" (Exhibit 12), all described below, were made by me and the other assistant chemists. This access is evidenced by Mr. Uthira Kumar's entries into the common notebook in his handwriting describing the experiments entitled "PDL/ACF/048/98," "PDL/ACF/051/98," "PDL/ACF/053/98," "PDL/ACF/055/98," "PDL/ACF/056/98" and "PDL/ACF/048/98" (collectively Exhibit 13), each of which was made

after the entries entitled "FURACA #04," "Furaca #06," "CEFTIOFUR #05" and "FURACA #10," and before November 27, 2000.

13. Mr. Uthira Kumar had knowledge about the separate laboratory notebook described in paragraph 11. Mr. Uthira Kumar's knowledge about the separate laboratory notebook is also evidenced in Exhibit 8. In reporting the "FURACA #03" experiment, Mr. Uthira Kumar initially used the title "N-15." This illustrates, at the very least, Mr. Uthira Kumar's knowledge about the separate laboratory notebook described in paragraph 11.

14. Before November 27, 2000, at Mr. Deshpande's and Dr. Das's instruction, the other assistant chemists and I carried out experiments in which a cephalosporin compound (furaca: 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) represented by formula (I),



(I)

was prepared by a process comprising:

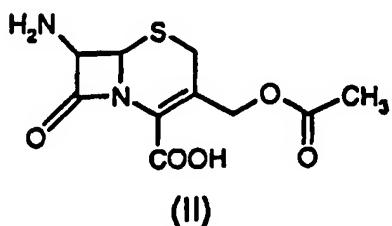
(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

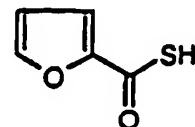
(ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) of the formula (III) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA) of the formula (II), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.



(II)



(III)

15. In a series of meetings with the assistant chemists, which took place before November 27, 2000, Mr. Deshpande instructed the assistant chemists to prepare furaca by combining (i) boron trifluoride (BF_3) in ethyl acetate and acetic acid as a mixture of organic solvents with (ii) 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) in which the TFA was prepared and with (iii) 7-aminocephalosporanic acid (7-ACA), to precipitate the resultant furaca, and to determine the yield and purity of the resultant furaca.

16. In accordance with the instructions that Mr. Deshpande gave the other assistant chemists and me at those meetings, before November 27, 2000, three of the other assistant chemists and I had performed experiments involving the preparation of furaca that had been described by Mr. Deshpande at the meetings. Those other assistant chemists were Messrs. Senthil Kumar, Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220) and Venkatachari Mukundan.

III. FURACA #03 EXPERIMENT

17. Exhibit 8 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #03," reflecting an experiment performed by Mr. Uthira Kumar at Mr. Deshpande's direction before November 27, 2000.

18. Mr. Deshpande met with Mr. Uthira Kumar and discussed the process described in the following paragraphs 20-22 prior to performance of the experiment "FURACA #03." I was aware of Mr. Deshpande's meetings with Mr. Uthira Kumar to give him such instructions, and contemporaneously observed Mr. Uthira Kumar's entries in the common notebook relating to the process performed in the experiment "FURACA #03."

19. Exhibit 8 describes in two stages the preparation of furaca carried out by Mr. Uthira Kumar in accordance with the instructions given to him by Mr. Deshpande, in handwriting that I recognize as Mr. Uthira Kumar's handwriting and entered into the notebook by Mr. Uthira Kumar.

20. In the first stage, entitled "Preparation of TFA" in Exhibit 8, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 8 describes Mr. Deshpande's instructions to Mr. Uthira Kumar, in accordance with which:

- a. 700 ml of demineralized water (abbreviated "DMW") and 75.0 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT"), the mixture was stirred to obtain a clear solution and the charging funnel was flushed with an additional 30 ml of demineralized water;
- b. 46.0 ml of 2-furoyl chloride were added over 40-45 minutes (minutes

being abbreviated with the symbol "'") at 20-25°C and then stirred for an additional 5 minutes;

c. 500 ml of ethyl acetate (abbreviated "EtOAC") was then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 10-15 minutes;

d. the resulting organic layer (abbreviated "OL₁") and aqueous layer were separated;

e. an additional 350 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-25°C;

f. the organic and aqueous layers were again separated; and 200 ml of ethyl acetate was added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by addition of 1:1 hydrochloric acid at 20-25°C;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") containing the produced TFA was kept for the next stage.

21. In the second stage, entitled "Preparation of Furaca" in Exhibit 8, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in the first stage, and

- (iii) 7-aminocephalosporanic acid (7-ACA), and
(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

22. In particular, Exhibit 8 describes Mr. Deshpande's instructions to Mr. Uthira Kumar, in accordance with which:

- a. 103.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into a mix of boron trifluoride (BF_3) catalyst-purged ethyl acetate (abbreviated "EtOAc") and acetic acid (abbreviated "HOAc") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 20°C;
- b. 260.0 ml of the TFA solution prepared in the first stage (i.e. a solution of 2-thiofuroic acid in the solvent ethyl acetate) were added to the resulting mixture;
- c. the temperature was maintained at 30°C for two hours;
- d. after completion of the reaction, the reaction mass was then transferred into 300.0 ml of demineralized water precooled to 15°C, along with 2.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");
- e. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated "NH₃") solution at 20-25°C over 25-30 minutes;
- f. the product was stirred for 30 minutes at 20-25°C; and
- g. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate.

23. Mr. Deshpande met with Mr. Uthira Kumar and discussed the results of the experiment "FURACA #03" following completion of that experiment. I was aware of Mr.

Deshpande's meetings with Mr. Uthira Kumar to follow up on such experiments, and observed Mr. Uthira Kumar's entries in the common notebook relating to the results obtained in the experiment "FURACA #03." I saw these entries in the common notebook within one day after they were made as I made my own entries in that notebook.

24. As all of the instructions for preparing furaca as described in the experiment "FURACA #03" were provided to Mr. Uthira Kumar by Mr. Deshpande, I believe that Mr. Uthira Kumar learned the process described in paragraphs 20-22 from Mr. Deshpande.

25. I have reviewed and understand claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 8). The subject matter of those claims appears in all significant respects to be the subject matter that Mr. Deshpande instructed Mr. Uthira Kumar to carry out as described in paragraphs 20-22 above, and that he recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided to Mr. Uthira Kumar and reflected in the common notebook.

26. In particular, the instructions that Mr. Deshpande gave Mr. Uthira Kumar that are reflected in Exhibit 8 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating

furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

IV. FURACA #04 EXPERIMENT

27. Exhibit 9 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #04," reflecting an experiment performed by me at Mr. Deshpande's direction before November 27, 2000.

28. Mr. Deshpande met with me and discussed the process described in the following paragraphs 30-32 prior to performance of the experiment "FURACA #04."

29. Exhibit 9 describes in two stages the preparation of furaca carried out by me in accordance with the instructions given to me by Mr. Deshpande, in my handwriting and entered into the notebook by me.

30. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 9, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 9 correctly describes that, as Mr. Deshpande had instructed:

- a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g. of

sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;

- b. the solution was stirred at room temperature to get a clear solution;
- c. 23.0 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol " ' ") at 20-25°C and then stirred for an additional 5 minutes;
- d. 250 ml of ethyl acetate (abbreviated "EtOAC") were then charged into the solution, and the pH of the resulting solution was adjusted to 1.0-0.9 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 10-15 minutes;
- e. the resulting organic and aqueous layers were separated, and the organic layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 9, in a Table headed by "R/M" (abbreviating "Reaction Monitoring"), "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the HPLC analysis showed that the organic layer OL₁ contained 97.78 % pure TFA.
- f. an additional 175 ml of demineralized water was then charged to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-25°C over 10-15 minutes;
- g. the organic and aqueous layers were again separated; and 100 ml of ethyl acetate were charged to the aqueous layer (here abbreviated "aq. layer" and on the next page abbreviated "AL₂"), and the pH was adjusted to 1.0-0.9 by 1:1 hydrochloric acid at 20-25°C;
- h. the aqueous layer was subjected to HPLC and, as reported in the Table on

the next page of Exhibit 9, the HPLC analysis showed that the aqueous layer AL₂ contained 99.41 % pure TFA;

- i. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to HPLC; as reported in the Table on the next page of Exhibit 9, the HPLC analysis showed that the organic layer OL₃ contained 99.39 % pure TFA;
- j. the organic phase containing TFA in ethyl acetate (an organic solvent), with a volume of 132.0 ml, was kept for the next stage.

31. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 9, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,
 - (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and
 - (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

32. In particular, Exhibit 9 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into a mix of boron trifluoride (BF₃) catalyst-purged ethyl acetate (abbreviated "EtOAc")

and acetic acid (abbreviated "HOAc") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 15°C;

b. the solution was stirred for 5 minutes at 15°C, at which point 132.0 ml of the TFA solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were added (i.e., combined with the other components) and the temperature was raised to 30°C;

c. the temperature was maintained at 30°C until the reaction (abbreviated "rxn") was completed;

d. the reaction mass was then transferred into 600.0 ml of demineralized water at 15°C, and 1.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") was added for decolorization of the reaction mass;

e. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 18-20% ammonia (abbreviated " NH_3 ") solution at 20-25°C over 25-30 minutes;

f. the product was stirred for 30 minutes at 20-25°C; and

g. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate. As reported in Exhibit 9, the dry weight of the resulting furaca was 43.72 g, it had a moisture content ("M/C") of 2.31 and purity of the furaca was assayed and found to be 93.98%. The identity of the obtained furaca was confirmed by comparing with a working standard.

33. Mr. Deshpande met with me and discussed the results of the experiment "FURACA #04" following completion of that experiment before November 27, 2000.

34. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande

instructed me to carry out as described in paragraphs 30-32 above, and that I reported in the common notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that were provided to me by Mr. Deshpande and reflected in the common notebook.

35. In particular, the instructions that Mr. Deshpande gave me that are reflected in Exhibit 9 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic Acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

V. FURACA #06 EXPERIMENT

36. Exhibit 10 is a copy of sequential pages from the aforementioned common

laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Furaca #06," reflecting an experiment performed by Messrs. Mukundan and Senthil Kumar at Mr. Deshpande's direction before November 27, 2000. Mr. Deshpande gave the instructions to Messrs. Mukundan and Senthil Kumar to carry out this experiment.

37. Mr. Deshpande met with Messrs. Mukundan and Senthil Kumar and discussed the process described in the following paragraphs 39-41 prior to and after performance of the experiment "Furaca #06."

38. Exhibit 10 accurately describes in two stages the preparation of furaca carried out by Messrs. Mukundan and Senthil Kumar and me in accordance with the instructions given to us by Mr. Deshpande, in Messrs. Mukundan's and Senthil Kumar's respective handwritings and entered into the notebook by Messrs. Mukundan and Senthil Kumar (I contemporaneously wrote in the "OL₃" entry on the second page of the "Furaca #06" report).

39. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 10, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;

b. 27.5 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol "'") at 20-25°C and then the solution was stirred for an

additional 5 minutes;

c. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 15-20 minutes;

d. the resulting organic and aqueous layers were separated, and the organic layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 10, in a Table headed "Reaction Monitoring," "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained 98.17% pure 2-thiofuroic acid.

e. an additional 175 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") in 15-20 minutes, and the mixture was then stirred at 20-22°C over 30 minutes;

f. the organic and aqueous layers were again separated, 100 ml of ethyl acetate were added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by 1:1 hydrochloric acid;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the second page of Exhibit 10, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 96.5 % pure 2-thiofuroic acid;

h. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

40. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 10, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and
 - (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

41. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 200 ml of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container and the temperature was reduced to 0°C;
- b. the mixture was then purged with 68.5 g of boron trifluoride (BF_3) to form a catalyst solution of BF_3 in an organic solvent;
- c. 0.15 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") was then added to the container, and the mixture was stirred for 5 minutes;
- d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") followed by 130 ml of the 2-thiofuroic acid/ethyl acetate solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container with the catalyst solution of BF_3 in

an organic solvent and the mixture was stirred until completion of the reaction at 30°C;

e. separately, 150 ml of demineralized water were cooled to 15°C and 0.15 g of ethylenediaminetetraacetic acid were added to the water;

f. the reaction mass was then transferred into the demineralized water followed by addition of 1.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");

g. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated " NH_3 ") solution at 25-30°C over 40-45 minutes;

h. the product was stirred for 30 minutes at 20-25°C; and

i. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate. As reported in Exhibit 10, the wet weight of the resulting furaca was 116.8 g. The identity of the obtained furaca was confirmed by comparing with a working standard.

42. Mr. Deshpande met with Messrs. Mukundan and Senthil Kumar and discussed the results of the experiment "Furaca #06" following completion of that experiment before November 27, 2000.

43. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed Messrs. Mukundan and Senthil Kumar to carry out as described in paragraphs 39-41 above, and that we reported in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of

the instructions that Messrs. Mukundan and Senthil Kumar were provided by Mr. Deshpande and reflected in the common notebook.

44. In particular, the instructions that Mr. Deshpande gave Messrs. Mukundan and Senthil Kumar that are reflected in Exhibit 10 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

45. Mr. Senthil Kumar and I were both familiar with the results of the foregoing experiment "Furaca #06" (and we both took part in recording the procedures and results of the experiment in the common laboratory notebook) in preparation for the following "CEFTIOFUR #05" experiment, in which the product of the "Furaca #06" experiment was used to prepare ceftiofur before November 27, 2000.

VI. CEFTIOFUR #05 EXPERIMENT

46. Exhibit 11 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Ceftiofur #05," reflecting an experiment performed by Mr. Senthil Kumar and me at Mr. Deshpande's direction before November 27, 2000. Mr. Deshpande gave the instructions to Mr. Senthil Kumar and me to carry out this experiment.

47. Exhibit 11 describes the preparation of ceftiofur carried out by Mr. Senthil Kumar and me in accordance with the instructions given to us by Mr. Deshpande, in Mr. Senthil Kumar's and my handwriting and entered into the notebook by Mr. Senthil Kumar and me.

48. In the experiment described in Exhibit 11, ceftiofur was synthesized using furaca that was obtained in the previous experiment entitled "Furaca #06" described in paragraphs 36-45 above. The experiment described in Exhibit 11 confirms that the furaca made in the experiment "Furaca #06" was useful in the manufacture of ceftiofur.

49. In particular, Exhibit 11 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 443.2 ml of demineralized water (abbreviated "DMW") and 500 g of tetrahydrofuran (abbreviated "THF") were charged into a container and the temperature was reduced to 5°C;
- b. 116.8 g of the furaca (abbreviating "(3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid)") obtained from "Furaca #06" experiment followed by 74.0 g of methoxyiminothiazole intermediate (abbreviated "MAEM") were charged into the container at 3-

5°C;

- c. 40 ml of triethylamine (abbreviated "TEA") were added over 3 hours at 3-5°C and the temperature was maintained until completion of the reaction;
- d. 750 ml of ethyl acetate (abbreviated "EtOAc") and 1.0 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") were charged into the container at 15°C over 15 minutes, and the layers were separated;
- e. the aqueous layer was extracted with 400 ml of ethyl acetate for 15 minutes and the layers were again separated;
- f. the organic layer was extracted with 200 ml of demineralized water and the layers were again separated, and the aqueous layer was combined with the rich aqueous layer from step e;
- g. 135.0 g of sodium chloride (abbreviated "NaCl") and 950 ml of tetrahydrofuran were added to the solution at 18-20°C;
- h. the pH of the solution was adjusted to 3.0-3.1 with concentrated hydrochloric acid (abbreviated "conc. HCl") at 18-20°C over 20-25 minutes, the layers were then separated and the aqueous phase was discarded;
- i. the organic phase was charcoalized at 18-20°C over 40 minutes;
- j. the solution was filtered and the bed was washed with 100 ml of tetrahydrofuran;
- k. the pH was adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C over 10-15 minutes;
- l. the solution was seeded with 1.0 g of ceftiofur hydrochloride (abbreviated

"CFUR HCl") and stirred at 18-20°C over 1 hour;

- m. the pH was again adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C;
- n. the solution was again seeded with 1.0 g of ceftiofur hydrochloride and stirred at 18-20°C over 1 hour;
- o. 450 ml of iso-propyl ether (abbreviated "IPE") were added to the solution at 18-20°C over 40 minutes;
- p. the solution was stirred at 18-20°C over 1 hour and then filtered;
- q. the filtrate was washed with 250 ml of isopropyl ether and dried, and 87.4 g of dry ceftiofur were obtained and purity of ceftiofur prepared by this process was assayed by HPLC and found to be 97.45%. The identity of the obtained ceftiofur was confirmed by comparing with a working standard.

VII. CONCLUSION

50. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date:

12 08 2003



Raja Jeya Kumar

Attachments:

- Exhibit 1 - Claims
- Exhibit 3 - U.S. Patent No. 6,476,220 B2
- Exhibit 8 - Pages from Common Laboratory Notebook
- Exhibit 9 - Pages from Common Laboratory Notebook
- Exhibit 10 - Pages from Common Laboratory Notebook
- Exhibit 11 - Pages from Common Laboratory Notebook
- Exhibit 13 - Pages from Common Laboratory Notebook



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

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TECH CENTER 1600/2900

RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, Bhausaheb Pandharinath KHADANGALE, aged 41 years, son of Pandharinath P. KHADANGALE, resident of Santhi Avenue, No. 7, Dr. Radhakrishnan Road, Thiruvanmiyur, Chennai - 600 041, Tamilnadu and citizen of India, hereby declare and state:

I. BACKGROUND

1. I have a Master's degree in Chemistry, which was conferred upon me by Pune University, in Pune, Maharashtra, India in 1986.

2. I have been employed by Orchid Chemicals and Pharmaceuticals Limited since 1995 and I have a total of 16 years of work and research experience in cephalosporin synthesis technology.

3. I am familiar with the above-captioned patent application, including the present claims of that application, which appear in Exhibit 1.

4. I am an inventor of the subject matter claimed in the above-captioned patent application.

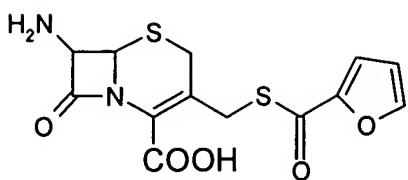
II. FURACA SYNTHESIS AT ORCHID

5. Since before 1995, it has been known that preparation of cephalosporin can be split into two stages: (A) formation of an intermediate "furaca" (3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid), and (B) conversion of furaca to cephalosporin.

6. During my tenure at Orchid, a team of senior scientists employed by Orchid was set up to work on such processes under the leadership of Dr. Gautam K. Das. Mr. Pramod N. Deshpande and Dr. Das were the core members of this team. I worked separately with Dr. Das.

7. Dr. Das met with Mr. Deshpande and Mr. Deshpande separately met with his assistant chemists to discuss Mr. Deshpande's, Dr. Das's and my ideas for improvement of processes for the production of cephalosporin. Mr. Deshpande instructed them as to the next work to be performed. Mr. Deshpande provided the details of the experiments to be performed, including the chemicals to be used, the amounts and proportions thereof, and the manner in which they were to be reacted. The assistant chemists performed most of the experiments, and reported the outcome of the experiments to Mr. Deshpande. Mr. Deshpande reported them to Dr. Das.

8. Before November 27, 2000, Mr. Deshpande, Dr. Das and I conceived of the invention described in the present claims of the above-captioned patent application, and we carried out experiments and/or instructed the assistant chemists to carry out experiments in which a cephalosporin compound (furaca: 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) represented by formula (I),



(I)

was prepared by a process comprising:

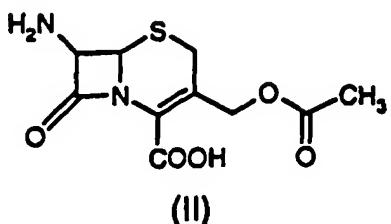
(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

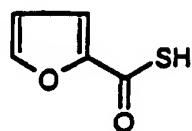
(ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) of the formula (III) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA) of the formula (II), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.



(II)



(III)

9. In a series of meetings with the assistant chemists, which took place before November 27, 2000, Mr. Deshpande instructed the assistant chemists to prepare furaca by combining boron trifluoride (BF₃) in ethyl acetate and acetic acid as a mixture of organic

solvents with 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) in which the TFA was prepared and with 7-aminocephalosporanic acid (7-ACA), to precipitate the resultant furaca, and to determine the yield and purity of the resultant furaca. Thus by the date of the first of those meetings, it was clear to me that Mr. Deshpande, Dr. Das and I had conceived of the method which Mr. Deshpande instructed the assistant chemists to perform.

10. In accordance with the instructions that Mr. Deshpande gave them at those meetings, before November 27, 2000, the assistant chemists had performed experiments involving the preparation of furaca that had been described by Mr. Deshpande at the meetings, and I was informed of the results of those experiments.

III. CONCLUSION

11 I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: 12 / 8 / 2003


Bhausaheb P. Khadangale

Attachments:

Exhibit 1 - Claims



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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AUG 18 2003

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In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, Pramod Narayan DESHPANDE, aged 45 years, son of Narayan Gangadhar Deshpande resident of No. 5-Temple Glade Apartments, 41-D, Beach Road, Kalakshetra Colony, Besant Nagar, Chennai 600 090, Tamilnadu and citizen of India, hereby declare and state:

I. BACKGROUND

1. I have a Master's degree in Chemistry, which was conferred upon me by Pune University, in Pune, Maharastra, India in 1980.

2. I have been employed by Orchid Chemicals and Pharmaceuticals Limited since 1997 and I have a total of 22 years of work and research experience in cephalosporin synthesis technology.

3. I am familiar with the above-captioned patent application, including the present claims of that application, which appear in Exhibit 1.

4. I am an inventor of the subject matter claimed in the above-captioned patent application.

II. ORCHID CHEMICALS AND PHARMACEUTICALS LIMITED

5. Orchid Chemicals and Pharmaceuticals Limited ("Orchid"), the assignee of the above-captioned patent application (see Exhibit 2, which is an assignment of the invention and application to Orchid), was founded in 1994 in India (which has been a WTO country since 1995). In that year, Orchid set up a Research and Development unit equipped with state-of-the art facilities to undertake and conduct research on pharmaceuticals on a laboratory scale, a pilot scale and for commercial viability, including a state-of-the art and highly reliable reagent, chemicals and equipment supply department in which high quality reagents, chemicals and equipment were kept available for use in Orchid's day-to-day work. Since at least 1995, Orchid has been vigorously implementing research projects on cephalosporin antibiotics such as Cephalexin, Cefpodoxime, Cefdinir, Cefadroxil and Ceftiofur.

6. The Orchid Research and Development unit has been given the ISO 2002 Certification for maintaining excellent manufacturing and quality systems.

7. As part of its intensive and successful efforts to produce cephalosporin antibiotics, Orchid has engaged in development of innovative processes whereby cephalosporins can be manufactured economically on a commercial scale.

III. FURACA SYNTHESIS AT ORCHID

8. Since before 1995, it has been known that preparation of cephalosporin can be split into two stages: (A) formation of an intermediate "furaca" (3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid), and (B) conversion of furaca to cephalosporin.

9. At the time that I joined Orchid in 1997, a team of senior scientists employed by Orchid was being set up to work on such processes under the leadership of Dr. Gautam Das. Dr. Das (who worked with Mr. Bhausaheb P. Khadangale) and I were the core members of this team. Assistant chemists helped us by performing experiments as instructed by Dr. Das and me. These assistant chemists included, *inter alia*, Mr. Senthil Kumar, Mr. Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220 (Exhibit 3)), Mr. Raja Jeya Kumar, Mr. Venkatachari Mukundan and Mr. S. Srinivasan. Mr. Uthira Kumar was employed by Orchid and worked in my laboratory during the course of all of the experiments described herein.

10. The laboratory in which I supervised the assistant chemists was a small laboratory. Generally, no more than four to five assistant chemists worked in the laboratory at any one time. The assistant chemists routinely discussed the experiments that they were carrying out with each other. Such discussions were particularly common when the assistant chemists were working on the same or related experiments.

11. Dr. Das and I were experienced chemists with substantial experience in the art of cephalosporin synthesis. The assistant chemists were much less experienced in this area. In particular, Mr. Uthira Kumar was a recent college graduate with no practical experience when he was hired to assist with the project. Mr. Uthira Kumar had only one year of experience as a trainee chemist at Orchid and less than a year of experience as a probationary chemist at Orchid when the invention was conceived and first reduced to practice by and on behalf of the core

members of the team as further detailed below. See Exhibit 4, which is a copy of Mr. Uthira Kumar's resume showing no prior employment at the time of his hiring by Orchid, and Exhibit 5, which is a copy of the offer letter to Mr. Uthira Kumar describing in sections 1 and 2 the training and probationary periods of Mr. Kumar's employment by Orchid. Exhibits 4 and 5 are both signed by Mr. Uthira Kumar, and are both business records kept in the ordinary course of business by Orchid.

12. On an almost daily basis, I met with Dr. Das and separately met with the assistant chemists to discuss Dr. Das's and my ideas for improvement of processes for the production of cephalosporin. At my meetings with the assistant chemists, they reviewed the outcome of the previous day's work and I instructed them as to the next work to be performed. I provided the details of the experiments to be performed, including the chemicals to be used, the amounts and proportions thereof, and the manner in which they were to be reacted. The assistant chemists performed most of the experiments, and reported the outcome of the experiments to me. I reported them to Dr. Das.

13. The assistant chemists only performed experiments that were expressly requested by Dr. Das and me. All significant parameters of such experiments were established by Dr. Das's and my instructions to the assistant chemists.

14. In accordance with Orchid's laboratory practices, the team members recorded most of the experiments that they carried out on the project in a common laboratory notebook. In addition, various preliminary experiments were recorded in a separate notebook that I maintained. Entries in the common laboratory notebook were given titles identifying the object product and an experiment number, e.g., "FURACA #03," "FURACA #04," "CEFTIOFUR #05." Entries in the separate notebook were given as titles alphanumeric experiment numbers

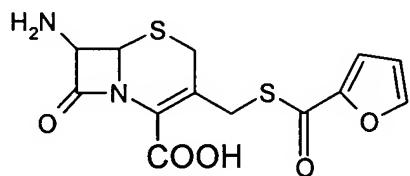
indicating the chronological position of an experiment in a sequence of experiments. In particular, the separate notebook included entries having "N" titles, e.g., "FURACA/N/03," "FURACA/N/04," etc., describing furaca synthesis via a "new route." This new route involved the novel use of a catalyst solution of boron trifluoride in an organic solvent or in a mixture of organic solvents, as further reduced to practice in the "Furaca" experiments described below.

15. Mr. Uthira Kumar had access to the common laboratory notebook described in paragraph 14 above during the course of all of the experiments described herein, and periodically made entries in the common laboratory notebook, as reflected by his handwriting, which I recognize therein. For example, the common notebook describes an experiment entitled "FURACA #03" (Exhibit 8) described below, which was conducted by Mr. Uthira Kumar and is reported in the common notebook in his handwriting. Mr. Uthira Kumar had access to and made entries in the common laboratory notebook after making his entry describing "FURACA #03," and after entries describing the experiments "FURACA #04" (Exhibit 9), "Furaca #06" (Exhibit 10), "CEFTIOFUR #05" (Exhibit 11), and "FURACA #10" (Exhibit 12), all described below, were made by other assistant chemists. This access is evidenced by Mr. Uthira Kumar's entries into the common notebook in his handwriting describing the experiments entitled "PDL/ACF/048/98," "PDL/ACF/051/98," "PDL/ACF/053/98," "PDL/ACF/055/98," "PDL/ACF/056/98" and "PDL/ACF/048/98" (collectively Exhibit 13), each of which was made after the entries entitled "FURACA #04," "Furaca #06," "CEFTIOFUR #05" and "FURACA #10," and before November 27, 2000.

16. Mr. Uthira Kumar had knowledge about the separate laboratory notebook described in paragraph 14. Mr. Uthira Kumar's knowledge about the separate laboratory notebook is also evidenced in Exhibit 8. In reporting the "FURACA #03" experiment, Mr.

Uthira Kumar initially used the title "N-15." This illustrates, at the very least, Mr. Uthira Kumar's knowledge about the separate laboratory notebook described in paragraph 14.

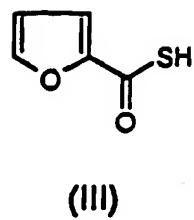
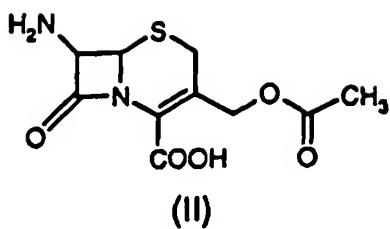
17. Before November 27, 2000, Dr. Das, Mr. Khadangale and I conceived of the invention described in the present claims of the above-captioned patent application, and we carried out experiments and/or instructed the assistant chemists to carry out experiments in which a cephalosporin compound (furaca: 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) represented by formula (I),



(I)

was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) of the formula (III) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA) of the formula (II), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.



18. In a series of meetings with the assistant chemists, which took place before November 27, 2000, I instructed the assistant chemists to prepare furaca by combining (i) boron trifluoride (BF_3) in ethyl acetate and acetic acid as a mixture of organic solvents with (ii) 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) in which the TFA was prepared and with (iii) 7-aminocephalosporanic acid (7-ACA), to precipitate the resultant furaca, and to determine the yield and purity of the resultant furaca. Thus by the date of the first of those meetings, it was clear to me that Dr. Das and I had conceived of the method which I instructed the assistant chemists to perform.

19. In accordance with the instructions that I gave them at those meetings, within a period of seventeen days, all of which were before November 27, 2000, Mr. Senthil Kumar had performed experiments involving the preparation of furaca that had been described by me. Subsequently, the other assistant chemists Messrs. Uthira Kumar (one of the named "inventors" of U.S. Patent No. 6,476,220), Raja Jeya Kumar and Venkatachari Mukundan, in addition to Mr. Senthil Kumar, had carried out similar experiments that had been described by me.

IV. FURACA/N/06 EXPERIMENT

20. Exhibit 6 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time

period before November 27, 2000) including a section entitled "FURACA/N/06," reflecting an experiment performed by Mr. Senthil Kumar at my direction before November 27, 2000.

21. I met with Mr. Senthil Kumar and discussed the process described in the following paragraphs 23-24 prior to performance of the experiment "FURACA/N/06."

22. In Exhibit 6, the section entitled "FURACA/N/06" describes the preparation of furaca in a representative experiment carried out by Mr. Senthil Kumar in accordance with the instructions given to him by me, in my handwriting and entered into the notebook by me.

23. In the "FURACA/N/06" experiment in Exhibit 6, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

24. In particular, the section entitled "FURACA/N/06" in Exhibit 6 correctly describes that, in accordance with my instructions:

a. 25.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") and 92 g of a mixture of boron trifluoride (BF_3) and acetic acid (abbreviated "Ac") were added to 75 ml of ethyl acetate -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a

mixture of the organic solvents ethyl acetate and acetic acid -- at 35°C;

b. 90 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/05") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 2 hours and 30 minutes at 40°C;

c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with sodium hydrogen sulfite (abbreviated "hydro");

d. the pH of the water/reaction mass mixture was then adjusted to 4.5 with ammonia (abbreviated "NH₃") solution at 20°C;

e. solid furaca was precipitated from the reaction mixture, and filtered. As reported in the section entitled "FURACA/N/06" in Exhibit 6, the dry weight of the resulting furaca was 25.1 g, it had a moisture content (abbreviated "M/c") of 1.44% and the purity of the furaca was assayed and found to be 96.54%. The identity of the obtained furaca was confirmed by comparing with a working standard.

25. I met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA/N/06" following completion of that experiment before November 27, 2000.

26. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that I instructed Mr. Senthil Kumar to carry out as described in paragraphs 23-24 above, and that I recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic

chemistry synthesis laboratory) at the time in view of the instructions that I provided Mr. Senthil Kumar reflected in the separate notebook.

27. In particular, the instructions that I gave Mr. Senthil Kumar that are reflected in the section entitled "FURACA/N/06" in Exhibit 6 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

V. FURACA/N/07 EXPERIMENT

28. Exhibit 6 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/07," reflecting an experiment performed by Mr. Senthil Kumar at my direction before November 27, 2000.

29. I met with Mr. Senthil Kumar and discussed the process described in the

following paragraphs 31-32 prior to performance of the experiment "FURACA/N/07."

30. In Exhibit 6, the section entitled "FURACA/N/07" describes in the preparation of furaca in a representative experiment carried out by Mr. Senthil Kumar in accordance with the instructions given to him by me, in my handwriting and entered into the notebook by me.

31. In the "FURACA/N/07" experiment in Exhibit 6, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

32. In particular, the section entitled "FURACA/N/07" in Exhibit 6 correctly describes that, in accordance with my instructions:

a. 25.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") was combined with 185 ml of an ethyl acetate/boron trifluoride (BF_3) stock solution and 15 ml of acetic acid (abbreviated "Ac") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid;

b. 90 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/05") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent)

was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 4 hours and 30 minutes at 40°C;

- c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with sodium hydrogen sulfite (abbreviated "hydro");
- d. the pH of the water/reaction mass mixture was then adjusted to 4.5 with ammonia (abbreviated "NH₃") solution at 20°C;
- e. solid furaca was precipitated from the reaction mixture, and filtered.

As reported in the section entitled "FURACA/N/07" in Exhibit 6, the dry weight of the resulting furaca was 24.8 g, it had a moisture content (abbreviated "M/c") of 2.0% and the purity of the furaca was assayed and found to be 97.48%. The identity of the obtained furaca was confirmed by comparing with a working standard.

33. I met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA/N/07" following completion of that experiment before November 27, 2000.
34. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that I instructed Mr. Senthil Kumar to carry out as described in paragraphs 31-32 above, and that I recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that I provided Mr. Senthil Kumar reflected in the separate notebook.

35. In particular, the instructions that I gave Mr. Senthil Kumar that are reflected in the section entitled "FURACA/N/07" in Exhibit 6 specifically identified a process to prepare

furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VI. FURACA/N/12 EXPERIMENT

36. Exhibit 7 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/12," reflecting an experiment performed by Mr. Senthil Kumar at my direction before November 27, 2000.

37. I met with Mr. Senthil Kumar and discussed the process described in the following paragraphs 39-40 prior to performance of the experiment "FURACA/N/12."

38. In Exhibit 7, the section entitled "FURACA/N/12" describes the preparation of furaca in a representative experiment carried out by Mr. Senthil Kumar in accordance with the instructions given to him by me, in my handwriting and entered into the notebook by me.

39. In the "FURACA/N/12" experiment in Exhibit 7, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

- (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

40. In particular, the section entitled "FURACA/N/12" in Exhibit 7 correctly describes that, in accordance with my instructions:

- a. 100.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were added to a mixture of 700 ml ethyl acetate, 60 ml acetic acid and 140 g boron trifluoride (BF_3) -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 25°C;
- b. 252 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/12") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 1 hour and 30 minutes at 40°C;
- c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with 2.0 g sodium hydrogen sulfite (abbreviated "hydro");

d. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 185 ml of ammonia (abbreviated "NH₃") solution at 25°C;

e. solid furaca was precipitated from the reaction mixture, and filtered and washed. As reported in section entitled "FURACA/N/12" in Exhibit 7, the dry weight of the resulting furaca was 116.3 g and the purity of the furaca was assayed and found to be 97.73%. The identity of the obtained furaca was confirmed by comparing with a working standard.

41. I met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA/N/12" following completion of that experiment before November 27, 2000.

42. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that I instructed Mr. Senthil Kumar to carry out as described in paragraphs 39-40 above, and that I recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that I provided Mr. Senthil Kumar reflected in the separate notebook.

43. In particular, the instructions that I gave Mr. Senthil Kumar that are reflected in the section entitled "FURACA/N/12" in Exhibit 7 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further

called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VII. FURACA #03 EXPERIMENT

44. Exhibit 8 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #03," reflecting an experiment performed by Mr. Uthira Kumar at my direction before November 27, 2000.

45. I met with Mr. Uthira Kumar and discussed the process described in the following paragraphs 47-49 prior to performance of the experiment "FURACA #03."

46. Exhibit 8 describes in two stages the preparation of furaca carried out by Mr. Uthira Kumar in accordance with the instructions given to him by me, in Mr. Uthira Kumar's handwriting and entered into the notebook by Mr. Uthira Kumar.

47. In the first stage, entitled "Preparation of TFA" in Exhibit 8, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 8 correctly describes my instructions to Mr. Uthira Kumar, in accordance with which:

a. 700 ml of demineralized water (abbreviated "DMW") and 75.0 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room

temperature (abbreviated "RT"), the mixture was stirred to obtain a clear solution and the charging funnel was flushed with an additional 30 ml of demineralized water;

b. 46.0 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol "'") at 20-25°C and then stirred for an additional 5 minutes;

c. 500 ml of ethyl acetate (abbreviated "EtOAC") was then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 10-15 minutes;

d. the resulting organic layer (abbreviated "OL₁") and aqueous layer were separated;

e. an additional 350 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-25°C;

f. the organic and aqueous layers were again separated; and 200 ml of ethyl acetate was added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by addition of 1:1 hydrochloric acid at 20-25°C;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") containing the produced TFA was kept for the next stage.

48. In the second stage, entitled "Preparation of Furaca" in Exhibit 8, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in the first stage, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

49. In particular, Exhibit 8 correctly describes my instructions to Mr. Uthira Kumar, in accordance with which:

a. 103.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into a mix of boron trifluoride (BF_3) catalyst-purged ethyl acetate (abbreviated "EtOAc") and acetic acid (abbreviated "HOAc") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 20°C;

b. 260.0 ml of the TFA solution prepared in the first stage (i.e. a solution of 2-thiofuroic acid in the solvent ethyl acetate) were added to the resulting mixture;

c. the temperature was maintained at 30°C for two hours;

d. after completion of the reaction, the reaction mass was then transferred into 300.0 ml of demineralized water precooled to 15°C, along with 2.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");

e. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated "NH₃") solution at 20-25°C over 25-30 minutes;

f. the product was stirred for 30 minutes at 20-25°C; and

g. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate.

50. I met with Mr. Uthira Kumar and discussed the results of the experiment

"FURACA #03" following completion of that experiment.

51. As all of the instructions for preparing furaca as described in the experiment "FURACA #03" were provided to Mr. Uthira Kumar by me, Mr. Uthira Kumar learned the process described in paragraphs 47-49 from me before November 27, 2000.

52. I have reviewed and understand claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3). The subject matter of those claims appears in all significant respects to be the subject matter that I instructed Mr. Uthira Kumar to carry out as described in paragraphs 47-49 above, and that he recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that I provided to Mr. Uthira Kumar and reflected in the common notebook.

53. In particular, the instructions that I gave Mr. Uthira Kumar that are reflected in Exhibit 8 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions

reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VIII. FURACA #04 EXPERIMENT

54. Exhibit 9 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #04," reflecting an experiment performed by Mr. Raja Jeya Kumar at my direction before November 27, 2000.

55. I met with Mr. Raja Jeya Kumar and discussed the process described in the following paragraphs 57-59 prior to performance of the experiment "FURACA #04."

56. Exhibit 9 describes in two stages the preparation of furaca carried out by Mr. Raja Jeya Kumar in accordance with the instructions given to him by me, in Mr. Raja Jeya Kumar's handwriting and entered into the notebook by Mr. Raja Jeya Kumar.

57. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 9, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 9 correctly describes that, as I had instructed:

- a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g. of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;
- b. the solution was stirred at room temperature to get a clear solution;
- c. 23.0 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol " ' ") at 20-25°C and then stirred for an additional 5 minutes;

d. 250 ml of ethyl acetate (abbreviated "EtOAC") were then charged into the solution, and the pH of the resulting solution was adjusted to 1.0-0.9 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 10-15 minutes;

e. the resulting organic and aqueous layers were separated, and the organic layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 9, in a Table headed by "R/M" (abbreviating "Reaction Monitoring"), "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the HPLC analysis showed that the organic layer OL₁ contained 97.78 % pure TFA.

f. an additional 175 ml of demineralized water was then charged to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-25°C over 10-15 minutes;

g. the organic and aqueous layers were again separated; and 100 ml of ethyl acetate were charged to the aqueous layer (here abbreviated "aq. layer" and on the next page abbreviated "AL₂"), and the pH was adjusted to 1.0-0.9 by 1:1 hydrochloric acid at 20-25°C;

h. the aqueous layer was subjected to HPLC and, as reported in the Table on the next page of Exhibit 9, the HPLC analysis showed that the aqueous layer AL₂ contained 99.41 % pure TFA;

i. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to HPLC; as reported in the Table on the next page of Exhibit 9, the HPLC analysis showed that the organic layer OL₃ contained 99.39 % pure TFA;

j. the organic phase containing TFA in ethyl acetate (an organic solvent), with a volume of 132.0 ml, was kept for the next stage.

58. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 9, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

- (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,
 - (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and
 - (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

59. In particular, Exhibit 9 correctly describes that, in accordance with my instructions:

- a. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into a mix of boron trifluoride (BF_3) catalyst-purged ethyl acetate (abbreviated "EtOAc") and acetic acid (abbreviated "HOAc") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 15°C;
- b. the solution was stirred for 5 minutes at 15°C, at which point 132.0 ml of the TFA solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were added (i.e., combined with the other components) and the temperature was raised to 30°C;
- c. the temperature was maintained at 30°C until the reaction (abbreviated "rxn") was completed;
- d. the reaction mass was then transferred into 600.0 ml of demineralized

water at 15°C, and 1.0 g of sodium hydrogen sulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") was added for decolorization of the reaction mass;

e. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 18-20% ammonia (abbreviated " NH_3 ") solution at 20-25°C over 25-30 minutes;

f. the product was stirred for 30 minutes at 20-25°C; and

g. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate. As reported in Exhibit 9, the dry weight of the resulting furaca was 43.72 g, it had a moisture content ("M/C") of 2.31 and purity of the furaca was assayed and found to be 93.98%. The identity of the obtained furaca was confirmed by comparing with a working standard.

60. I met with Mr. Raja Jeya Kumar and discussed the results of the experiment "FURACA #04" following completion of that experiment before November 27, 2000.

61. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that I instructed Mr. Raja Jeya Kumar to carry out as described in paragraphs 57-59 above, and that he recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that I provided Mr. Raja Jeya Kumar reflected in the common notebook.

62. In particular, the instructions that I gave Mr. Raja Jeya Kumar that are reflected in Exhibit 9 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl

acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic Acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

IX. FURACA #06 EXPERIMENT

63. Exhibit 10 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Furaca #06," reflecting an experiment performed by Messrs. Mukundan and Senthil Kumar at my direction before November 27, 2000. I gave the instructions to Messrs. Mukundan and Senthil Kumar to carry out this experiment.

64. I met with Messrs. Mukundan and Senthil Kumar and discussed the process described in the following paragraphs 66-68 prior to and after performance of the experiment "Furaca #06."

65. Exhibit 10 describes in two stages the preparation of furaca carried out by Messrs. Mukundan and Senthil Kumar in accordance with the instructions given to them by me, in Messrs. Mukundan's and Senthil Kumar's respective handwritings and entered into the notebook

by Messrs. Mukundan and Senthil Kumar (Mr. Raja Jeya Kumar contemporaneously wrote in the "OL₃" entry on the second page of the "Furaca #06" report).

66. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 10, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 10 correctly describes that, in accordance with my instructions:

- a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;
- b. 27.5 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol "'") at 20-25°C and then the solution was stirred for an additional 5 minutes;
- c. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 15-20 minutes;
- d. the resulting organic and aqueous layers were separated, and the organic layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 10, in a Table headed "Reaction Monitoring," "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained 98.17% pure 2-thiofuroic acid.
- e. an additional 175 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated

"NaHCO₃") in 15-20 minutes, and the mixture was then stirred at 20-22°C over 30 minutes;

f. the organic and aqueous layers were again separated, 100 ml of ethyl acetate were added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by 1:1 hydrochloric acid;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the second page of Exhibit 10, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 96.5 % pure 2-thiofuroic acid;

h. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

67. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 10, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

68. In particular, Exhibit 10 correctly describes that, in accordance with my instructions:

- a. 200 ml of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container and the temperature was reduced to 0°C;
- b. the mixture was then purged with 68.5 g of boron trifluoride (BF_3) to form a catalyst solution of BF_3 in an organic solvent;
- c. 0.15 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") was then added to the container, and the mixture was stirred for 5 minutes;
- d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") followed by 130 ml of the 2-thiofuroic acid/ethyl acetate solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container with the catalyst solution of BF_3 in an organic solvent and the mixture was stirred until completion of the reaction at 30°C;
- e. separately, 150 ml of demineralized water were cooled to 15°C and 0.15 g of ethylenediaminetetraacetic acid were added to the water;
- f. the reaction mass was then transferred into the demineralized water followed by addition of 1.0 g of sodium hydrogen sulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");
- g. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated " NH_3 ") solution at 25-30°C over 40-45 minutes;
- h. the product was stirred for 30 minutes at 20-25°C; and
- i. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate. As reported in Exhibit 10, the wet weight of the resulting furaca was 116.8 g. The identity of the obtained furaca was confirmed by comparing with a working standard.

69. I met with Messrs. Mukundan and Senthil Kumar and discussed the results of the experiment "Furaca #06" following completion of that experiment before November 27, 2000.

70. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that I instructed Messrs. Mukundan and Senthil Kumar to carry out as described in paragraphs 66-68 above, and that they recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Messrs. Mukundan and Senthil Kumar were provided by me and reflected in the common notebook.

71. In particular, the instructions that I gave Messrs. Mukundan and Senthil Kumar that are reflected in Exhibit 10 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

72. Messrs. Senthil Kumar and Raja Jeya Kumar were both familiar with the results of the foregoing experiment "Furaca #06" (we both took part in recording the procedures and results of the experiment in the common laboratory notebook) in preparation for the following "CEFTIOFUR #05" experiment, in which the product of the "Furaca #06" experiment was used to prepare ceftiofur before November 27, 2000.

X. CEFTIOFUR #05 EXPERIMENT

73. Exhibit 11 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Ceftiofur #05," reflecting an experiment performed by Messrs. Raja Jeya Kumar and Senthil Kumar at my direction before November 27, 2000. I gave the instructions to Messrs. Raja Jeya Kumar and Senthil Kumar to carry out this experiment.

74. Exhibit 11 describes the preparation of ceftiofur carried out by Messrs. Raja Jeya Kumar and Senthil Kumar in accordance with the instructions given to them by me, in Messrs. Raja Jeya Kumar and Senthil Kumar's handwriting and entered into the notebook by Messrs. Raja Jeya Kumar and Senthil Kumar.

75. In the experiment described in Exhibit 11, ceftiofur was synthesized using furaca that was obtained in the previous experiment entitled "Furaca #06" described in paragraphs 63-72 above. The experiment described in Exhibit 11 confirms that the furaca made in the experiment "Furaca #06" was useful in the manufacture of ceftiofur.

76. In particular, Exhibit 11 correctly describes that, in accordance with my instructions:

- a. 443.2 ml of demineralized water (abbreviated "DMW") and 500 g of tetrahydrofuran (abbreviated "THF") were charged into a container and the temperature was reduced to 5°C;
- b. 116.8 g of the furaca (abbreviating "(3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid)") obtained from "Furaca #06" experiment followed by 74.0 g of methoxyiminothiazole intermediate (abbreviated "MAEM") were charged into the container at 3-5°C;
- c. 40 ml of triethylamine (abbreviated "TEA") were added over 3 hours at 3-5°C and the temperature was maintained until completion of the reaction;
- d. 750 ml of ethyl acetate (abbreviated "EtOAc") and 1.0 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") were charged into the container at 15°C over 15 minutes, and the layers were separated;
- e. the aqueous layer was extracted with 400 ml of ethyl acetate for 15 minutes and the layers were again separated;
- f. the organic layer was extracted with 200 ml of demineralized water and the layers were again separated, and the aqueous layer was combined with the rich aqueous layer from step e;
- g. 135.0 g of sodium chloride (abbreviated "NaCl") and 950 ml of tetrahydrofuran were added to the solution at 18-20°C;
- h. the pH of the solution was adjusted to 3.0-3.1 with concentrated hydrochloric acid (abbreviated "conc. HCl") at 18-20°C over 20-25 minutes, the layers were then separated and the aqueous phase was discarded;
- i. the organic phase was charcoalized at 18-20°C over 40 minutes;

- j. the solution was filtered and the bed was washed with 100 ml of tetrahydrofuran;
- k. the pH was adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C over 10-15 minutes;
 - l. the solution was seeded with 1.0 g of ceftiofur hydrochloride (abbreviated "CFUR HCl") and stirred at 18-20°C over 1 hour;
 - m. the pH was again adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C;
 - n. the solution was again seeded with 1.0 g of ceftiofur hydrochloride and stirred at 18-20°C over 1 hour;
 - o. 450 ml of iso-propyl ether (abbreviated "IPE") were added to the solution at 18-20°C over 40 minutes;
 - p. the solution was stirred at 18-20°C over 1 hour and then filtered;
 - q. the filtrate was washed with 250 ml of isopropyl ether and dried, and 87.4 g of dry ceftiofur were obtained and purity of ceftiofur prepared by this process was assayed by HPLC and found to be 97.45%. The identity of the obtained ceftiofur was confirmed by comparing with a working standard.

XI. FURACA #10 EXPERIMENT

77. Exhibit 12 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #10," reflecting an experiment performed by Mr. Senthil Kumar at my direction before November 27, 2000. I gave the

instructions to Mr. Senthil Kumar to carry out this experiment.

78. I met with Mr. Senthil Kumar and discussed the process described in the following paragraphs 80-82 prior to performance of the experiment "FURACA #10."

79. Exhibit 12 describes in two stages the preparation of furaca carried out by Mr. Senthil Kumar in accordance with the instructions given to him by me, in Mr. Senthil Kumar's handwriting and entered into the notebook by Mr. Senthil Kumar.

80. In the first stage, entitled "Stage I: Preparation of TFA" in Exhibit 12, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 12 correctly describes that, as I had instructed:

a. 365 ml of demineralized water (abbreviated "DMW") were charged into a container and the temperature was reduced to 20-25°C;

b. 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into the container and the mixture was stirred for 5 minutes (minutes being abbreviated with the symbol "'") to obtain a clear solution;

c. 27.5 g of 2-furoyl chloride were added over 40-45 minutes at 20-25°C and then stirred while maintaining temperature for 10 minutes;

d. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 22-25°C over 15 minutes;

e. the resulting organic and aqueous layers were separated, and the aqueous layer was discarded; the organic layer (abbreviated "OL₁") was subjected to high performance liquid chromatography; as reported in the Table on the first page of Exhibit 12, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained

97.34 % pure 2-thiofuroic acid;

f. an additional 175 ml of demineralized water were then added to the organic layer, and the pH was adjusted to 7.0 to 7.1 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-22°C over 15 minutes;

g. the mixture was then stirred at 20-22°C over 30 minutes, and then the organic and aqueous layers were again separated;

h. 100 ml of ethyl acetate were added to the aqueous layer and the pH was adjusted to 0.9-1.0 by adding 1:1 hydrochloric acid at 20-22°C over 15 minutes;

i. the mixture was stirred at 20-22°C over 15 minutes, and then the organic and aqueous layers were again separated;

j. the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the first page of Exhibit 12, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 97.48 % pure 2-thiofuroic acid;

k. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

81. In the second stage, entitled "STAGE II: FURACA PREPARATION" in Exhibit 12, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

82. In particular, Exhibit 12 correctly describes that, in accordance with my instructions:

- a. 200 g of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container at room temperature (abbreviated "RT") and the temperature was reduced to 0°C;
- b. the mixture was then purged with 68.5 g of boron trifluoride (BF_3) gas at less than 10°C;
- c. 0.3 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") were then added to the container, and the mixture was stirred for 5 minutes at 15°C;
- d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into the container with the catalyst solution of boron trifluoride and organic solvents and stirred for 5 minutes, and then 130 ml of the 2-thiofuroic acid solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container (i.e., combined with the other components) and the mixture was stirred until for 2.5 hours at 30°C, the resulting reaction mass was divided equally into two parts;
- e. the first part of the reaction mass was charged into 75.0 ml of demineralized water precooled to 15°C, 0.15 g of ethylenediaminetetraacetic acid and 0.5 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") were then added;

- f. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 18-20% ammonia (abbreviated "NH₃") solution at 25-30°C over 40-45 minutes;
- g. the mixture was stirred for 30 minutes at 25°C and then filtered;
- h. the filtrate was washed by spray, slurry and spray with demineralized water;
- i. the wet reaction mass was transferred to a round bottom flask (abbreviated "RBF"), 75 ml of ethyl acetate were added, the mixture was stirred for 15 minutes at 25°C and then filtered;
- j. the filtrate was washed by spray with 25 ml of ethyl acetate;
- k. the product was dried for 2-3 hours at 30-35°C and analyzed, 28.4 g of dry furaca were obtained with quantitative purity of 91.93, the identity of the obtained furaca was confirmed by comparing with a working standard;
- l. the second part of the reaction mass was charged into 75.0 ml of demineralized water precooled to 15°C, 0.15 g of ethylenediaminetetraacetic acid and 0.5 g of sodium hydrosulfite (Na₂S₂O₅ -- abbreviated "SHS") were then added;
- m. the pH of the water/reaction mass mixture was then adjusted to 3.0 with 18-20% ammonia (abbreviated "NH₃") solution at 25-30°C over 40-45 minutes;
- n. the mixture was stirred for 30 minutes at 25°C and then filtered;
- o. the filtrate was washed by spray, slurry and spray with demineralized water;
- p. the wet reaction mass was transferred to a round bottom flask (abbreviated "RBF"), 75 ml of ethyl acetate were added, the mixture was stirred for 15 minutes at 25°C and then filtered;

q. the filtrate was washed by spray with 25 ml of ethyl acetate;
r. the product was dried for 2-3 hours at 30-35°C and analyzed, 29.5 g of dry furaca were obtained with quantitative purity of 81.84. The identity of the obtained furaca was confirmed by comparing with a working standard.

83. I met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA #10" following completion of that experiment before November 27, 2000.

84. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that I instructed Mr. Senthil Kumar to carry out as described in paragraphs 80-82 above, and that he recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that I provided Mr. Senthil Kumar and reflected in the common notebook.

85. In particular, the instructions that I gave Mr. Senthil Kumar that are reflected in Exhibit 12 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic Acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art

would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

XII. BATCH PROCESSING EXPERIMENTS

86. After completion of the experiments described above, but still before November 27, 2000, commercial feasibility of the process detailed in paragraph 17 above was tested by repeating the entire set of experiments on a commercial scale in the plant for large-scale studies, before November 27, 2000. The process passed all tests, and proved to be economical.

87. Exhibit 14 is a Batch Processing Record for a large scale performance of the process described in paragraph 17 above, as well as large scale preparation of ceftiofur from the product of that process, also dated before November 27, 2000, signed by Mr. K.C. Pathak and me. The processes described in Exhibit 14 were carried out under the supervision of Mr. Pathak (then Head of Production for Orchid) and me (then Head of the Orchid Process Development Laboratory and one of the inventors of the above-captioned patent application). The work described in Exhibit 14 was carried out in the presence and under the direct supervision of Dr. Ashwani Kumar, who signed it as Shift Supervisor, by the individuals who initialed in the column "Sign of Shift Chemist/Operator" for each step of the process.

88. Exhibit 14 correctly describes, in its first phase, the details of an actual large scale production of furaca by combining (i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent (ethyl acetate), (ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent ethyl acetate, and (iii) 7-aminocephalosporanic acid (7-ACA), and allowing them to

react, and precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid, according to the process developed by Dr. Das, Mr. Khadangale and me.

89. In particular, steps 1-20 of the procedure outlined on the first two pages of the portion of Exhibit 14 entitled "Batch Processing - Furaca Preparation" describe the preparation of 2-thiofuroic acid (TFA) as a reactant for the ensuing process of producing furaca. As described in Exhibit 14, water, sodium sulfide, furoyl chloride and ethyl acetate were combined (see steps 1-8) and stirred and allowed to settle into organic and aqueous layers (see steps 9-12). After several separation steps (see steps 13-28), the product TFA in ethyl acetate (an organic solvent) was collected (see step 29 and step 38).

90. Then a solution of boron trifluoride (BF_3) in ethyl acetate (an organic solvent) was prepared (see steps 31-36), and combined with 7-ACA and the previously prepared TFA-in-a-solvent (see steps 37-38), and the mixture was allowed to react at about 30°C (see steps 39-40). The reaction was monitored by high performance liquid chromatography ("HPLC"), particularly with respect to the produced furaca (abbreviated "ACF") and the reactants 7-ACA and TFA, and the reaction monitoring data was recorded on page 3 of Exhibit 14. Thereafter, solid furaca (ACF) was precipitated and recovered as a mill cake (see steps 41-62). The product furaca was thereafter washed (see steps 1-20 on page 6 of the portion of Exhibit 14 entitled "Batch Processing - Furaca Preparation"). The obtained furaca was assayed by HPLC and confirmed by comparing with a working standard.

91. Exhibit 14 also correctly describes, in its second and third phases, the further processing of the furaca product obtained in the first phase of batch processing and actual large scale production of ceftiofur using that furaca product. The preparation of ceftiofur using the obtained furaca confirms the usefulness of the furaca as an intermediate in the manufacture of

ceftiofur.

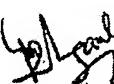
92. The portion of Exhibit 14 entitled "Batch Processing Record - Extraction of Fluorides from ML" describes the further processing of the furaca product obtained in the first phase by extraction of fluorides. The portion of Exhibit 14 entitled "Batch Processing Record - Ceftiofur Hydrochloride" describes the manufacture of ceftiofur using that furaca product. The obtained ceftiofur product was assayed by HPLC and its identity was confirmed by comparing with a working standard.

93. This process was ultimately put into commercial production at Orchid.

CONCLUSION

94. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

12-08-03


Pramod N. Deshpande

Attachments:

- | | |
|-----------|--|
| Exhibit 1 | - Claims |
| Exhibit 2 | - Assignment |
| Exhibit 3 | - U.S. Patent No. 6,476,220 B2 |
| Exhibit 4 | - Uthira Kumar Resume |
| Exhibit 5 | - Uthira Kumar Offer Letter |
| Exhibit 6 | - Page from Separate Laboratory Notebook |

- Exhibit 7 - Page from Separate Laboratory Notebook
- Exhibit 8 - Pages from Common Laboratory Notebook
- Exhibit 9 - Pages from Common Laboratory Notebook
- Exhibit 10 - Pages from Common Laboratory Notebook
- Exhibit 11 - Pages from Common Laboratory Notebook
- Exhibit 12 - Pages from Common Laboratory Notebook
- Exhibit 13 - Pages from Common Laboratory Notebook
- Exhibit 14 - Batch Processing Record



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Pramod N. DESHPANDE et al.

Group Art Unit: 1624

Application No.: 10/035,178

Examiner: M. Berch

Filed: January 4, 2002

Docket No.: 113299

For: SYNTHESIS OF CEFTIOFUR INTERMEDIATE

RECEIVED
AUG 18 2003
TECH CENTER 1600/2900

RULE 608(b) DECLARATION (37 C.F.R. §1.608(b))

I, Gautam Kumar DAS, aged 50 years son of Pashupati Das, resident of Geetha Apartments, No. 33, Rukmini Road, Kalakshetra colony, Besant Nagar, Chennai – 600 090, and a citizen of India, hereby declare and state:

I. BACKGROUND

1. I have a Master's Degree in Chemistry which was conferred upon me by Calcutta University in Calcutta in the year 1974 and doctoral degree in chemistry which was conferred upon me by Indian Institute Of Technology, Kharagpur in the year 1981.
2. I have been employed by Orchid Chemicals and Pharmaceuticals Limited since 1995 and I have a total of 22 years of work and research experience in cephalosporin synthesis technology.

3. I am familiar with the above-captioned patent application, including the present claims of that application, which appear in Exhibit 1.

4. I am an inventor of the subject matter claimed in the above-captioned patent application.

II. ORCHID CHEMICALS AND PHARMACEUTICALS LIMITED

5. Orchid Chemicals and Pharmaceuticals Limited ("Orchid"), the assignee of the above-captioned patent application (see Exhibit 2, which is an assignment of the invention and application to Orchid), was founded in 1994 in India (which has been a WTO country since 1995). In that year, Orchid set up a Research and Development unit equipped with state-of-the art facilities to undertake and conduct research on pharmaceuticals on a laboratory scale, a pilot scale and for commercial viability, including a state-of-the art and highly reliable reagent, chemicals and equipment supply department in which high quality reagents, chemicals and equipment were kept available for use in Orchid's day-to-day work. Since at least 1995, Orchid has been vigorously implementing research projects on cephalosporin antibiotics such as Cephalexin, Cefpodoxime, Cefdinir, Cefadroxil and Ceftiofur.

6. The Orchid Research and Development unit has been given the ISO 2002 Certification for maintaining excellent manufacturing and quality systems.

7. As part of its intensive and successful efforts to produce cephalosporin antibiotics, Orchid has engaged in development of innovative processes whereby cephalosporins can be manufactured economically on a commercial scale.

III. FURACA SYNTHESIS AT ORCHID

8. Since before 1995, it has been known that preparation of cephalosporin can be split into two stages: (A) formation of an intermediate "furaca" (3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid), and (B) conversion of furaca to cephalosporin.

9. In 1997, a team of senior scientists employed by Orchid was being set up to work on such processes under my leadership. Mr. Pramod N. Deshpande and I were the core members of this team. I worked separately with Mr. Bhausaheb P. Khadangale. Assistant chemists helped us by performing experiments as instructed by Mr. Deshpande and me. These assistant chemists included, *inter alia*, Mr. Senthil Kumar, Mr. Uthira Kumar (named as an "inventor" on U.S. Patent No. 6,476,220 (Exhibit 3)), Mr. Raja Jeya Kumar, Mr. Venkatachari Mukundan and Mr. S. Srinivasan. Mr. Uthira Kumar was employed by Orchid and worked in the laboratory during the course of all of the experiments described herein.

10. The laboratory in which Mr. Deshpande supervised the assistant chemists was a small laboratory. Generally, no more than four to five assistant chemists worked in the laboratory at any one time. The assistant chemists routinely discussed the experiments that they were carrying out with each other. Such discussions were particularly common when the assistant chemists were working on the same or related experiments.

11. Mr. Deshpande and I were experienced chemists with substantial experience in the art of cephalosporin synthesis. The assistant chemists were much less experienced in this area. In particular, Mr. Uthira Kumar was a recent college graduate with no practical experience when he was hired to assist with the project. Mr. Uthira Kumar had only one year of experience as a trainee chemist at Orchid and less than a year of experience as a probationary chemist at Orchid when the invention was conceived and first reduced to practice by and on behalf of the

core members of the team as further detailed below. See Exhibit 4, which is a copy of Mr. Uthira Kumar's resume showing no prior employment at the time of his hiring by Orchid, and Exhibit 5, which is a copy of the offer letter to Mr. Uthira Kumar describing in sections 1 and 2 the training and probationary periods of Mr. Kumar's employment by Orchid. Exhibits 4 and 5 are both signed by Mr. Uthira Kumar, and are both business records kept in the ordinary course of business by Orchid.

12. On an almost daily basis, I met with Mr. Deshpande and he separately met with the assistant chemists to discuss Mr. Deshpande's and my ideas for improvement of processes for the production of cephalosporin. At Mr. Deshpande's meetings with the assistant chemists, they reviewed the outcome of the previous day's work and Mr. Deshpande instructed them as to the next work to be performed. Mr. Deshpande provided the details of the experiments to be performed, including the chemicals to be used, the amounts and proportions thereof, and the manner in which they were to be reacted. The assistant chemists performed most of the experiments, and reported the outcome of the experiments to Mr. Deshpande. Mr. Deshpande reported them to me.

13. The assistant chemists only performed experiments that were expressly requested by Mr. Deshpande and me. All significant parameters of such experiments were established by Mr. Deshpande's and my instructions to the assistant chemists.

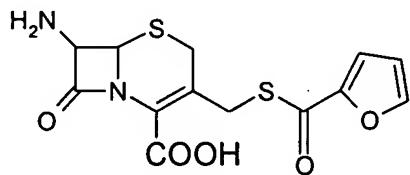
14. In accordance with Orchid's laboratory practices, the team members recorded most of the experiments that they carried out on the project in a common laboratory notebook. In addition, various preliminary experiments were recorded in a separate notebook that Mr. Deshpande maintained. Entries in the common laboratory notebook were given titles identifying the object product and an experiment number, e.g., "FURACA #03," "FURACA #04,"

"CEFTIOFUR #05." Entries in the separate notebook were given as titles alphanumeric experiment numbers indicating the chronological position of an experiment in a sequence of experiments. In particular, the separate notebook included entries having "N" titles, e.g., "FURACA/N/03," "FURACA/N/04," etc., describing furaca synthesis via a "new route." This new route involved the novel use of a catalyst solution of boron trifluoride in an organic solvent or in a mixture of organic solvents, as further reduced to practice in the "Furaca" experiments described below.

15. Mr. Uthira Kumar had access to the common laboratory notebook described in paragraph 14 above during the course of all of the experiments described herein, and periodically made entries in the common laboratory notebook, as reflected by his handwriting, which I recognize therein. For example, the common notebook describes an experiment entitled "FURACA #03" (Exhibit 8) described below, which was conducted by Mr. Uthira Kumar and is reported in the common notebook in his handwriting. Mr. Uthira Kumar had access to and made entries in the common laboratory notebook after making his entry describing "FURACA #03," and after entries describing the experiments "FURACA #04" (Exhibit 9), "Furaca #06" (Exhibit 10), "CEFTIOFUR #05" (Exhibit 11), and "FURACA #10" (Exhibit 12), all described below, were made by other assistant chemists. This access is evidenced by Mr. Uthira Kumar's entries into the common notebook in his handwriting describing the experiments entitled "PDL/ACF/048/98," "PDL/ACF/051/98," "PDL/ACF/053/98," "PDL/ACF/055/98," "PDL/ACF/056/98" and "PDL/ACF/048/98" (collectively Exhibit 13), each of which was made after the entries entitled "FURACA #04," "Furaca #06," "CEFTIOFUR #05" and "FURACA #10," and before November 27, 2000.

16. Mr. Uthira Kumar had knowledge about the separate laboratory notebook described in paragraph 14. Mr. Uthira Kumar's knowledge about the separate laboratory notebook is also evidenced in Exhibit 8. In reporting the "FURACA #03" experiment, Mr. Uthira Kumar initially used the title "N-15." This illustrates, at the very least, Mr. Uthira Kumar's knowledge about the separate laboratory notebook described in paragraph 14.

17. Before November 27, 2000, Mr. Deshpande, Mr. Khadangale and I conceived of the invention described in the present claims of the above-captioned patent application, and we carried out experiments and/or instructed the assistant chemists to carry out experiments in which a cephalosporin compound (furaca: 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) represented by formula (I),

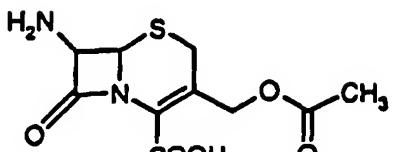


(I)

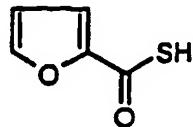
was prepared by a process comprising:

- (a) combining the following components:
 - (i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,
 - (ii) a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) of the formula (III) in a solvent, and
 - (iii) 7-aminocephalosporanic acid (7-ACA) of the formula (II), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.



(II)



(III)

18. In a series of meetings with the assistant chemists, which took place before November 27, 2000, Mr. Deshpande instructed the assistant chemists to prepare furaca by combining (i) boron trifluoride (BF_3) in ethyl acetate and acetic acid as a mixture of organic solvents with (ii) 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) in which the TFA was prepared and with (iii) 7-aminocephalosporanic acid (7-ACA), to precipitate the resultant furaca, and to determine the yield and purity of the resultant furaca. Thus by the date of the first of those meetings, it was clear to me that Mr. Deshpande and I had conceived of the method which Mr. Deshpande instructed the assistant chemists to perform.

19. In accordance with the instructions that Mr. Deshpande gave them at those meetings, within a period of seventeen days, all of which were before November 27, 2000, Mr. Senthil Kumar had performed experiments involving the preparation of furaca that had been described by me. Subsequently, the other assistant chemists Messrs. Uthira Kumar (one of the named "inventors" of U.S. Patent No. 6,476,220), Raja Jeya Kumar and Venkatachari Mukundan, in addition to Mr. Senthil Kumar, had carried out similar experiments that had been described by Mr. Deshpande.

IV. FURACA/N/06 EXPERIMENT

20. Exhibit 6 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/06," reflecting an experiment performed by Mr. Senthil Kumar at Mr. Deshpande's direction before November 27, 2000.

21. Mr. Deshpande met with Mr. Senthil Kumar and discussed the process described in the following paragraphs 23-24 prior to performance of the experiment "FURACA/N/06."

22. In Exhibit 6, the section entitled "FURACA/N/06" describes the preparation of furaca in a representative experiment carried out by Mr. Senthil Kumar in accordance with the instructions given to him by Mr. Deshpande, in Mr. Deshpande's handwriting and entered into the notebook by Mr. Deshpande.

23. In the "FURACA/N/06" experiment in Exhibit 6, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

24. In particular, the section entitled "FURACA/N/06" in Exhibit 6 correctly describes that, in accordance with Mr. Deshpande's instructions:
- a. 25.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") and 92 g of a mixture of boron trifluoride (BF_3) and acetic acid (abbreviated "Ac") were added to 75 ml of ethyl acetate -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 35°C;
 - b. 90 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/05") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 2 hours and 30 minutes at 40°C;
 - c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with sodium hydrogen sulfite (abbreviated "hydro");
 - d. the pH of the water/reaction mass mixture was then adjusted to 4.5 with ammonia (abbreviated " NH_3 ") solution at 20°C;
 - e. solid furaca was precipitated from the reaction mixture, and filtered. As reported in the section entitled "FURACA/N/06" in Exhibit 6, the dry weight of the resulting furaca was 25.1 g, it had a moisture content (abbreviated "M/c") of 1.44% and the purity of the furaca was assayed and found to be 96.54%. The identity of the obtained furaca was confirmed by comparing with a working standard.

25. Mr. Deshpande met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA/N/06" following completion of that experiment before November 27, 2000.

26. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed Mr. Senthil Kumar to carry out as described in paragraphs 23-24 above, and that Mr. Deshpande recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided Mr. Senthil Kumar reflected in the separate notebook.

27. In particular, the instructions that Mr. Deshpande gave Mr. Senthil Kumar that are reflected in the section entitled "FURACA/N/06" in Exhibit 6 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

V. FURACA/N/07 EXPERIMENT

28. Exhibit 6 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/07," reflecting an experiment performed by Mr. Senthil Kumar at Mr. Deshpande's direction before November 27, 2000.

29. Mr. Deshpande met with Mr. Senthil Kumar and discussed the process described in the following paragraphs 31-32 prior to performance of the experiment "FURACA/N/07."

30. In Exhibit 6, the section entitled "FURACA/N/07" describes in the preparation of furaca in a representative experiment carried out by Mr. Senthil Kumar in accordance with the instructions given to him by Mr. Deshpande, in Mr. Deshpande's handwriting and entered into the notebook by Mr. Deshpande.

31. In the "FURACA/N/07" experiment in Exhibit 6, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

32. In particular, the section entitled "FURACA/N/07" in Exhibit 6 correctly describes that, in accordance with Mr. Deshpande's instructions:
- a. 25.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") was combined with 185 ml of an ethyl acetate/boron trifluoride (BF_3) stock solution and 15 ml of acetic acid (abbreviated "Ac") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid;
 - b. 90 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/05") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 4 hours and 30 minutes at 40°C;
 - c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with sodium hydrogen sulfite (abbreviated "hydro");
 - d. the pH of the water/reaction mass mixture was then adjusted to 4.5 with ammonia (abbreviated " NH_3 ") solution at 20°C;
 - e. solid furaca was precipitated from the reaction mixture, and filtered.

As reported in the section entitled "FURACA/N/07" in Exhibit 6, the dry weight of the resulting furaca was 24.8 g, it had a moisture content (abbreviated "M/c") of 2.0% and the purity of the furaca was assayed and found to be 97.48%. The identity of the obtained furaca was confirmed by comparing with a working standard.

33. Mr. Deshpande met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA/N/07" following completion of that experiment before November 27, 2000.

34. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed Mr. Senthil Kumar to carry out as described in paragraphs 31-32 above, and that Mr. Deshpande recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided Mr. Senthil Kumar reflected in the separate notebook.

35. In particular, the instructions that Mr. Deshpande gave Mr. Senthil Kumar that are reflected in the section entitled "FURACA/N/07" in Exhibit 6 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VI. FURACA/N/12 EXPERIMENT

36. Exhibit 7 is a copy of a page from the aforementioned separate laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) including a section entitled "FURACA/N/12," reflecting an experiment performed by Mr. Senthil Kumar at Mr. Deshpande's direction before November 27, 2000.

37. Mr. Deshpande met with Mr. Senthil Kumar and discussed the process described in the following paragraphs 39-40 prior to performance of the experiment "FURACA/N/12."

38. In Exhibit 7, the section entitled "FURACA/N/12" describes the preparation of furaca in a representative experiment carried out by Mr. Senthil Kumar in accordance with the instructions given to him by Mr. Deshpande, in Mr. Deshpande's handwriting and entered into the notebook by Mr. Deshpande.

39. In the "FURACA/N/12" experiment in Exhibit 7, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF_3) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

40. In particular, the section entitled "FURACA/N/12" in Exhibit 7 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 100.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were added to a mixture of 700 ml ethyl acetate, 60 ml acetic acid and 140 g boron trifluoride (BF_3) -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 25°C;
- b. 252 ml of a solution of 2-thiofuroic acid in ethyl acetate (abbreviated "TFA/N/12") obtained in a previous experiment (i.e. a solution of 2-thiofuroic acid in a solvent) was added to the mixture (i.e., combined with the other components) and the mixture was stirred for 1 hour and 30 minutes at 40°C;
- c. the resulting reaction mass was then transferred into 500 ml of demineralized water at 15°C along with 2.0 g sodium hydrogen sulfite (abbreviated "hydro");
- d. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 185 ml of ammonia (abbreviated " NH_3 ") solution at 25°C;
- e. solid furaca was precipitated from the reaction mixture, and filtered and washed. As reported in section entitled "FURACA/N/12" in Exhibit 7, the dry weight of the resulting furaca was 116.3 g and the purity of the furaca was assayed and found to be 97.73%. The identity of the obtained furaca was confirmed by comparing with a working standard.

41. Mr. Deshpande met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA/N/12" following completion of that experiment before November 27, 2000.

42. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande

instructed Mr. Senthil Kumar to carry out as described in paragraphs 39-40 above, and that Mr. Deshpande recorded in the separate notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided Mr. Senthil Kumar reflected in the separate notebook.

43. In particular, the instructions that Mr. Deshpande gave Mr. Senthil Kumar that are reflected in the section entitled "FURACA/N/12" in Exhibit 7 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 40°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious." Thus the instructions reflected in the separate notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VII. FURACA #03 EXPERIMENT

44. Exhibit 8 is a copy of sequential pages from the aforementioned common

laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #03," reflecting an experiment performed by Mr. Uthira Kumar at Mr. Deshpande's direction before November 27, 2000.

45. Mr. Deshpande met with Mr. Uthira Kumar and discussed the process described in the following paragraphs 47-49 prior to performance of the experiment "FURACA #03."

46. Exhibit 8 describes in two stages the preparation of furaca carried out by Mr. Uthira Kumar in accordance with the instructions given to him by Mr. Deshpande, in Mr. Uthira Kumar's handwriting and entered into the notebook by Mr. Uthira Kumar.

47. In the first stage, entitled "Preparation of TFA" in Exhibit 8, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 8 correctly describes Mr. Deshpande's instructions to Mr. Uthira Kumar, in accordance with which:

a. 700 ml of demineralized water (abbreviated "DMW") and 75.0 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT"), the mixture was stirred to obtain a clear solution and the charging funnel was flushed with an additional 30 ml of demineralized water;

b. 46.0 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol "'") at 20-25°C and then stirred for an additional 5 minutes;

c. 500 ml of ethyl acetate (abbreviated "EtOAC") was then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 10-15 minutes;

d. the resulting organic layer (abbreviated "OL₁") and aqueous layer were separated;

e. an additional 350 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-25°C;

f. the organic and aqueous layers were again separated; and 200 ml of ethyl acetate was added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0 by addition of 1:1 hydrochloric acid at 20-25°C;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") containing the produced TFA was kept for the next stage.

48. In the second stage, entitled "Preparation of Furaca" in Exhibit 8, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in the first stage, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

49. In particular, Exhibit 8 correctly describes Mr. Deshpande's instructions to Mr. Uthira Kumar, in accordance with which:

a. 103.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into a mix of boron trifluoride (BF₃) catalyst-purged ethyl acetate (abbreviated "EtOAc")

and acetic acid (abbreviated "HOAc") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 20°C;

- b. 260.0 ml of the TFA solution prepared in the first stage (i.e. a solution of 2-thiofuroic acid in the solvent ethyl acetate) were added to the resulting mixture;
- c. the temperature was maintained at 30°C for two hours;
- d. after completion of the reaction, the reaction mass was then transferred into 300.0 ml of demineralized water precooled to 15°C, along with 2.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS");
- e. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated "NH₃") solution at 20-25°C over 25-30 minutes;
- f. the product was stirred for 30 minutes at 20-25°C; and
- g. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate.

50. Mr. Deshpande met with Mr. Uthira Kumar and discussed the results of the experiment "FURACA #03" following completion of that experiment.

51. As all of the instructions for preparing furaca as described in the experiment "FURACA #03" were provided to Mr. Uthira Kumar by Mr. Deshpande, Mr. Uthira Kumar learned the process described in paragraphs 47-49 from Mr. Deshpande before November 27, 2000.

52. I have reviewed and understand claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3). The subject matter of those claims appears in all significant respects to be the subject matter that Mr. Deshpande instructed Mr. Uthira Kumar to carry out as described in paragraphs 47-49 above, and that Mr. Uthira Kumar recorded in the common

notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Deshpande provided to Mr. Uthira Kumar and reflected in the common notebook.

53. In particular, the instructions that Mr. Deshpande gave Mr. Uthira Kumar that are reflected in Exhibit 8 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

VIII. FURACA #04 EXPERIMENT

54. Exhibit 9 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #04," reflecting an experiment

performed by Mr. Raja Jeya Kumar at Mr. Deshpande's direction before November 27, 2000.

55. Mr. Deshpande met with Mr. Raja Jeya Kumar and discussed the process described in the following paragraphs 57-59 prior to performance of the experiment "FURACA #04."

56. Exhibit 9 describes in two stages the preparation of furaca carried out by Mr. Raja Jeya Kumar in accordance with the instructions given to him by Mr. Deshpande, in Mr. Raja Jeya Kumar's handwriting and entered into the notebook by Mr. Raja Jeya Kumar.

57. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 9, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 9 correctly describes that, as Mr. Deshpande had instructed:

- a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g. of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;
- b. the solution was stirred at room temperature to get a clear solution;
- c. 23.0 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol " ' ") at 20-25°C and then stirred for an additional 5 minutes;
- d. 250 ml of ethyl acetate (abbreviated "EtOAC") were then charged into the solution, and the pH of the resulting solution was adjusted to 1.0-0.9 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 10-15 minutes;
- e. the resulting organic and aqueous layers were separated, and the organic layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 9, in a Table headed by "R/M"

(abbreviating "Reaction Monitoring"), "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the HPLC analysis showed that the organic layer OL₁ contained 97.78 % pure TFA.

f. an additional 175 ml of demineralized water was then charged to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-25°C over 10-15 minutes;

g. the organic and aqueous layers were again separated; and 100 ml of ethyl acetate were charged to the aqueous layer (here abbreviated "aq. layer" and on the next page abbreviated "AL₂"), and the pH was adjusted to 1.0-0.9 by 1:1 hydrochloric acid at 20-25°C;

h. the aqueous layer was subjected to HPLC and, as reported in the Table on the next page of Exhibit 9, the HPLC analysis showed that the aqueous layer AL₂ contained 99.41 % pure TFA;

i. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to HPLC; as reported in the Table on the next page of Exhibit 9, the HPLC analysis showed that the organic layer OL₃ contained 99.39 % pure TFA;

j. the organic phase containing TFA in ethyl acetate (an organic solvent), with a volume of 132.0 ml, was kept for the next stage.

58. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 9, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

- (ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and
- (iii) 7-aminocephalosporanic acid (7-ACA), and
- (b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

59. In particular, Exhibit 9 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into a mix of boron trifluoride (BF_3) catalyst-purged ethyl acetate (abbreviated "EtOAc") and acetic acid (abbreviated "HOAc") -- i.e., 7-ACA was combined with a catalyst solution of boron trifluoride in a mixture of the organic solvents ethyl acetate and acetic acid -- at 15°C;
- b. the solution was stirred for 5 minutes at 15°C, at which point 132.0 ml of the TFA solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were added (i.e., combined with the other components) and the temperature was raised to 30°C;
- c. the temperature was maintained at 30°C until the reaction (abbreviated "rxn") was completed;
- d. the reaction mass was then transferred into 600.0 ml of demineralized water at 15°C, and 1.0 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") was added for decolorization of the reaction mass;
- e. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 18-20% ammonia (abbreviated " NH_3 ") solution at 20-25°C over 25-30 minutes;
- f. the product was stirred for 30 minutes at 20-25°C; and
- g. solid furaca was precipitated, and was filtered out and washed with

demineralized water and ethyl acetate. As reported in Exhibit 9, the dry weight of the resulting furaca was 43.72 g, it had a moisture content ("M/C") of 2.31 and purity of the furaca was assayed and found to be 93.98%. The identity of the obtained furaca was confirmed by comparing with a working standard.

60. Mr. Deshpande met with Mr. Raja Jeya Kumar and discussed the results of the experiment "FURACA #04" following completion of that experiment before November 27, 2000.

61. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed Mr. Raja Jeya Kumar to carry out as described in paragraphs 57-59 above, and that Mr. Raja Jeya Kumar recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Raja Jeya Kumar was provided by Mr. Deshpande and reflected in the common notebook.

62. In particular, the instructions that Mr. Deshpande gave Mr. Raja Jeya Kumar that are reflected in Exhibit 9 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic Acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the

reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

IX. FURACA #06 EXPERIMENT

63. Exhibit 10 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Furaca #06," reflecting an experiment performed by Messrs. Mukundan and Senthil Kumar at Mr. Deshpande's direction before November 27, 2000. Mr. Deshpande gave the instructions to Messrs. Mukundan and Senthil Kumar to carry out this experiment.

64. Mr. Deshpande met with Messrs. Mukundan and Senthil Kumar and discussed the process described in the following paragraphs 66-68 prior to and after performance of the experiment "Furaca #06."

65. Exhibit 10 describes in two stages the preparation of furaca carried out by Messrs. Mukundan and Senthil Kumar in accordance with the instructions given to them by Mr. Deshpande, in Messrs. Mukundan and Senthil Kumar's respective handwritings and entered into the notebook by Messrs. Mukundan and Senthil Kumar (Mr. Raja Jeya Kumar contemporaneously wrote in the "OL₃" entry on the second page of the "Furaca #06" report).

66. In the first stage, entitled "Stage I Preparation of TFA" in Exhibit 10, a solution of

2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

- a. 350 ml of demineralized water (abbreviated "DMW") and 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into a container at room temperature (abbreviated "RT") and the charging funnel was flushed with an additional 15 ml of demineralized water;
- b. 27.5 ml of 2-furoyl chloride were added over 40-45 minutes (minutes being abbreviated with the symbol "'") at 20-25°C and then the solution was stirred for an additional 5 minutes;
- c. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 20-25°C over 15-20 minutes;
- d. the resulting organic and aqueous layers were separated, and the organic layer (abbreviated "OL₁") was subjected to analysis by high performance liquid chromatography (abbreviated "HPLC"). As reported on the next page of Exhibit 10, in a Table headed "Reaction Monitoring," "TFA" abbreviating 2-thiofuroic acid and "imp." abbreviating impurities, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained 98.17% pure 2-thiofuroic acid.
- e. an additional 175 ml of demineralized water were then added to the organic layer OL₁, and the pH was adjusted to 7.0 to 7.2 with sodium bicarbonate (abbreviated "NaHCO₃") in 15-20 minutes, and the mixture was then stirred at 20-22°C over 30 minutes;
- f. the organic and aqueous layers were again separated, 100 ml of ethyl acetate were added to the aqueous layer (abbreviated "AL₂"), and the pH was adjusted to 0.9-1.0

by 1:1 hydrochloric acid;

g. the organic and aqueous layers were again separated and the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the second page of Exhibit 10, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 96.5 % pure 2-thiofuroic acid;

h. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

67. In the second stage, entitled "Stage II Preparation of Furaca" in Exhibit 10, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

68. In particular, Exhibit 10 correctly describes that, in accordance with Mr. Deshpande's instructions:

a. 200 ml of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container and the temperature was reduced to 0°C;

b. the mixture was then purged with 68.5 g of boron trifluoride (BF₃) to form

a catalyst solution of BF₃ in an organic solvent;

c. 0.15 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") was then added to the container, and the mixture was stirred for 5 minutes;

d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") followed by 130 ml of the 2-thiofuroic acid/ethyl acetate solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container with the catalyst solution of BF₃ in an organic solvent and the mixture was stirred until completion of the reaction at 30°C;

e. separately, 150 ml of demineralized water were cooled to 15°C and 0.15 g of ethylenediaminetetraacetic acid were added to the water;

f. the reaction mass was then transferred into the demineralized water followed by addition of 1.0 g of sodium hydrosulfite (Na₂S₂O₅ -- abbreviated "SHS");

g. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 20% ammonia (abbreviated "NH₃") solution at 25-30°C over 40-45 minutes;

h. the product was stirred for 30 minutes at 20-25°C; and
i. solid furaca was precipitated, and was filtered out and washed with demineralized water and ethyl acetate. As reported in Exhibit 10, the wet weight of the resulting furaca was 116.8 g. The identity of the obtained furaca was confirmed by comparing with a working standard.

69. Mr. Deshpande met with Messrs. Mukundan and Senthil Kumar and discussed the results of the experiment "Furaca #06" following completion of that experiment before November 27, 2000.

70. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande

instructed Messrs. Mukundan and Senthil Kumar to carry out as described in paragraphs 66-68 above, and that Messrs. Mukundan and Senthil Kumar recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Messrs. Mukundan and Senthil Kumar were provided by Mr. Deshpande and reflected in the common notebook.

71. In particular, the instructions that Mr. Deshpande gave Messrs. Mukundan and Senthil Kumar that are reflected in Exhibit 10 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

72. Messrs. Senthil Kumar and Raja Jeya Kumar were both familiar with the results of the foregoing experiment "Furaca #06" (we both took part in recording the procedures and

results of the experiment in the common laboratory notebook) in preparation for the following "CEFTIOFUR #05" experiment, in which the product of the "Furaca #06" experiment was used to prepare ceftiofur before November 27, 2000.

X. CEFTIOFUR #05 EXPERIMENT

73. Exhibit 11 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "Ceftiofur #05," reflecting an experiment performed by Messrs. Raja Jeya Kumar and Senthil Kumar at Mr. Deshpande's direction before November 27, 2000. Mr. Deshpande gave the instructions to Messrs. Raja Jeya Kumar and Senthil Kumar to carry out this experiment.

74. Exhibit 11 describes the preparation of ceftiofur carried out by Messrs. Raja Jeya Kumar and Senthil Kumar in accordance with the instructions given to them by Mr. Deshpande, in Messrs. Raja Jeya Kumar and Senthil Kumar's handwriting and entered into the notebook by Messrs. Raja Jeya Kumar and Senthil Kumar.

75. In the experiment described in Exhibit 11, ceftiofur was synthesized using furaca that was obtained in the previous experiment entitled "Furaca #06" described in paragraphs 63-72 above. The experiment described in Exhibit 11 confirms that the furaca made in the experiment "Furaca #06" was useful in the manufacture of ceftiofur.

76. In particular, Exhibit 11 correctly describes that, in accordance with Mr. Deshpande's instructions:

a. 443.2 ml of demineralized water (abbreviated "DMW") and 500 g of tetrahydrofuran (abbreviated "THF") were charged into a container and the temperature was

reduced to 5°C;

- b. 116.8 g of the furaca (abbreviating "(3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid)") obtained from "Furaca #06" experiment followed by 74.0 g of methoxyiminothiazole intermediate (abbreviated "MAEM") were charged into the container at 3-5°C;
- c. 40 ml of triethylamine (abbreviated "TEA") were added over 3 hours at 3-5°C and the temperature was maintained until completion of the reaction;
- d. 750 ml of ethyl acetate (abbreviated "EtOAc") and 1.0 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") were charged into the container at 15°C over 15 minutes, and the layers were separated;
- e. the aqueous layer was extracted with 400 ml of ethyl acetate for 15 minutes and the layers were again separated;
- f. the organic layer was extracted with 200 ml of demineralized water and the layers were again separated, and the aqueous layer was combined with the rich aqueous layer from step e;
- g. 135.0 g of sodium chloride (abbreviated "NaCl") and 950 ml of tetrahydrofuran were added to the solution at 18-20°C;
- h. the pH of the solution was adjusted to 3.0-3.1 with concentrated hydrochloric acid (abbreviated "conc. HCl") at 18-20°C over 20-25 minutes, the layers were then separated and the aqueous phase was discarded;
- i. the organic phase was charcoalized at 18-20°C over 40 minutes;
- j. the solution was filtered and the bed was washed with 100 ml of tetrahydrofuran;

- k. the pH was adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C over 10-15 minutes;
- l. the solution was seeded with 1.0 g of ceftiofur hydrochloride (abbreviated "CFUR HCl") and stirred at 18-20°C over 1 hour;
- m. the pH was again adjusted to 0.9-1.0 with concentrated hydrochloric acid at 18-20°C;
- n. the solution was again seeded with 1.0 g of ceftiofur hydrochloride and stirred at 18-20°C over 1 hour;
- o. 450 ml of iso-propyl ether (abbreviated "IPE") were added to the solution at 18-20°C over 40 minutes;
- p. the solution was stirred at 18-20°C over 1 hour and then filtered;
- q. the filtrate was washed with 250 ml of isopropyl ether and dried, and 87.4 g of dry ceftiofur were obtained and purity of ceftiofur prepared by this process was assayed by HPLC and found to be 97.45%. The identity of the obtained ceftiofur was confirmed by comparing with a working standard.

XI. FURACA #10 EXPERIMENT

77. Exhibit 12 is a copy of sequential pages from the aforementioned common laboratory notebook, dated before November 27, 2000 (and in date sequence in the notebook at a time period before November 27, 2000) and entitled "FURACA #10," reflecting an experiment performed by Mr. Senthil Kumar at Mr. Deshpande's direction before November 27, 2000. Mr. Deshpande gave the instructions to Mr. Senthil Kumar to carry out this experiment.

78. Mr. Deshpande met with Mr. Senthil Kumar and discussed the process described

in the following paragraphs 80-82 prior to performance of the experiment "FURACA #10."

79. Exhibit 12 describes in two stages the preparation of furaca carried out by Mr. Senthil Kumar in accordance with the instructions given to him by Mr. Deshpande, in Mr. Senthil Kumar's handwriting and entered into the notebook by Mr. Senthil Kumar.

80. In the first stage, entitled "Stage I: Preparation of TFA" in Exhibit 12, a solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent was prepared. In particular, Exhibit 12 correctly describes that, as Mr. Deshpande had instructed:

- a. 365 ml of demineralized water (abbreviated "DMW") were charged into a container and the temperature was reduced to 20-25°C;
- b. 37.5 g of sodium hydrogen sulfite (abbreviated "NaSH") were charged into the container and the mixture was stirred for 5 minutes (minutes being abbreviated with the symbol "'") to obtain a clear solution;
- c. 27.5 g of 2-furoyl chloride were added over 40-45 minutes at 20-25°C and then stirred while maintaining temperature for 10 minutes;
- d. 250 ml of ethyl acetate (abbreviated "EtOAC") were then added to the solution, and the pH of the resulting solution was adjusted to 0.9-1.0 with 1:1 hydrochloric acid (abbreviated "HCl") at 22-25°C over 15 minutes;
- e. the resulting organic and aqueous layers were separated, and the aqueous layer was discarded; the organic layer (abbreviated "OL₁") was subjected to high performance liquid chromatography; as reported in the Table on the first page of Exhibit 12, the high performance liquid chromatography analysis showed that the organic layer OL₁ contained 97.34 % pure 2-thiofuroic acid;
- f. an additional 175 ml of demineralized water were then added to the

organic layer, and the pH was adjusted to 7.0 to 7.1 with sodium bicarbonate (abbreviated "NaHCO₃") at 20-22°C over 15 minutes;

g. the mixture was then stirred at 20-22°C over 30 minutes, and then the organic and aqueous layers were again separated;

h. 100 ml of ethyl acetate were added to the aqueous layer and the pH was adjusted to 0.9-1.0 by adding 1:1 hydrochloric acid at 20-22°C over 15 minutes;

i. the mixture was stirred at 20-22°C over 15 minutes, and then the organic and aqueous layers were again separated;

j. the organic layer (abbreviated "OL₃") was subjected to high performance liquid chromatography; as reported in the Table on the first page of Exhibit 12, the high performance liquid chromatography analysis showed that the organic layer OL₃ contained 97.48 % pure 2-thiofuroic acid;

k. the organic phase containing 2-thiofuroic acid in ethyl acetate (an organic solvent), with a volume of 130.0 ml, was kept for the next stage.

81. In the second stage, entitled "STAGE II: FURACA PREPARATION" in Exhibit 12, the cephalosporin compound furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) was prepared by a process comprising:

(a) combining the following components:

(i) a catalyst solution of boron trifluoride (BF₃) in an organic solvent or in a mixture of organic solvents,

(ii) the solution of 2-thiofuroic acid (furyl-2-carbonylthiol or TFA) in a solvent that had been prepared in Stage I, and

(iii) 7-aminocephalosporanic acid (7-ACA), and

(b) precipitating furaca (3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid) as a solid.

82. In particular, Exhibit 12 correctly describes that, in accordance with Mr. Deshpande's instructions:
- a. 200 g of ethyl acetate (an organic solvent) and 30 ml of glacial acetic acid (abbreviated "GAA") were charged into a container at room temperature (abbreviated "RT") and the temperature was reduced to 0°C;
 - b. the mixture was then purged with 68.5 g of boron trifluoride (BF_3) gas at less than 10°C;
 - c. 0.3 g of ethylenediaminetetraacetic acid (abbreviated "EDTA") were then added to the container, and the mixture was stirred for 5 minutes at 15°C;
 - d. 50.0 g of 7-aminocephalosporanic acid (abbreviated "7-ACA") were charged into the container with the catalyst solution of boron trifluoride and organic solvents and stirred for 5 minutes, and then 130 ml of the 2-thiofuroic acid solution prepared in Stage I (i.e. a solution of 2-thiofuroic acid in a solvent) were charged into the container (i.e., combined with the other components) and the mixture was stirred until for 2.5 hours at 30°C, the resulting reaction mass was divided equally into two parts;
 - e. the first part of the reaction mass was charged into 75.0 ml of demineralized water precooled to 15°C, 0.15 g of ethylenediaminetetraacetic acid and 0.5 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") were then added;
 - f. the pH of the water/reaction mass mixture was then adjusted to 3.5 with 18-20% ammonia (abbreviated " NH_3 ") solution at 25-30°C over 40-45 minutes;
 - g. the mixture was stirred for 30 minutes at 25°C and then filtered;

- h. the filtrate was washed by spray, slurry and spray with demineralized water;
- i. the wet reaction mass was transferred to a round bottom flask (abbreviated "RBF"), 75 ml of ethyl acetate were added, the mixture was stirred for 15 minutes at 25°C and then filtered;
- j. the filtrate was washed by spray with 25 ml of ethyl acetate;
- k. the product was dried for 2-3 hours at 30-35°C and analyzed, 28.4 g of dry furaca were obtained with quantitative purity of 91.93, the identity of the obtained furaca was confirmed by comparing with a working standard;
- l. the second part of the reaction mass was charged into 75.0 ml of demineralized water precooled to 15°C, 0.15 g of ethylenediaminetetraacetic acid and 0.5 g of sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_5$ -- abbreviated "SHS") were then added;
- m. the pH of the water/reaction mass mixture was then adjusted to 3.0 with 18-20% ammonia (abbreviated " NH_3 ") solution at 25-30°C over 40-45 minutes;
- n. the mixture was stirred for 30 minutes at 25°C and then filtered;
- o. the filtrate was washed by spray, slurry and spray with demineralized water;
- p. the wet reaction mass was transferred to a round bottom flask (abbreviated "RBF"), 75 ml of ethyl acetate were added, the mixture was stirred for 15 minutes at 25°C and then filtered;
- q. the filtrate was washed by spray with 25 ml of ethyl acetate;
- r. the product was dried for 2-3 hours at 30-35°C and analyzed, 29.5 g of dry furaca were obtained with quantitative purity of 81.84. The identity of the obtained furaca was

confirmed by comparing with a working standard.

83. Mr. Deshpande met with Mr. Senthil Kumar and discussed the results of the experiment "FURACA #10" following completion of that experiment before November 27, 2000.

84. The subject matter of claims 1-3 in column 4 of U.S. Patent No. 6,476,220 B2 (Exhibit 3) appears in all significant respects to be the subject matter that Mr. Deshpande instructed Mr. Senthil Kumar to carry out as described in paragraphs 80-82 above, and that Mr. Senthil Kumar recorded in the common notebook. To the extent that there are any differences, such differences and the described methods would have fully been obvious to anyone with ordinary skill in the art of furaca synthesis (e.g., a chemist with a post graduate chemistry degree and some experience in an organic chemistry synthesis laboratory) at the time in view of the instructions that Mr. Senthil Kumar were provided by Mr. Deshpande and reflected in the common notebook.

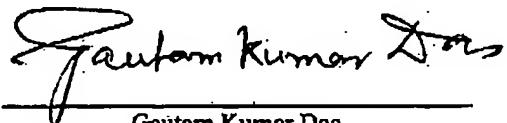
85. In particular, the instructions that Mr. Deshpande gave Mr. Senthil Kumar that are reflected in Exhibit 12 specifically identified a process to prepare furaca. The instructions called for preparation of a catalyst solution of boron trifluoride in a mixture of organic solvents (ethyl acetate and acetic acid). They further called for mixing that catalyst solution with a solution of 2-thiofuroic Acid (TFA) in a solvent (ethyl acetate) and 7-aminocephalosporanic acid (7-ACA), thereby reacting the 7-ACA with the reaction mixture. They further called for precipitating furaca from the reaction mixture as a solid. They further called for conducting the reaction step at 30°C, i.e., a temperature between 10 and 50°C. I believe that this describes everything that is recited in claims 1-3 of U.S. Patent No. 6,476,220 B2. In addition, one of ordinary skill in the art would have found selection of any order of combination of the reactants and the selection of

alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

CONCLUSION

86. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

12-08-2003


Gautam Kumar Das

Attachments:

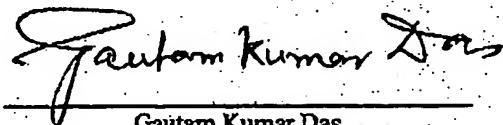
- Exhibit 1 - Claims
- Exhibit 2 - Assignment
- Exhibit 3 - U.S. Patent No. 6,476,220 B2
- Exhibit 4 - Uthira Kumar Resume
- Exhibit 5 - Uthira Kumar Offer Letter
- Exhibit 6 - Page from Separate Laboratory Notebook
- Exhibit 7 - Page from Separate Laboratory Notebook
- Exhibit 8 - Pages from Common Laboratory Notebook
- Exhibit 9 - Pages from Common Laboratory Notebook
- Exhibit 10 - Pages from Common Laboratory Notebook
- Exhibit 11 - Pages from Common Laboratory Notebook
- Exhibit 12 - Pages from Common Laboratory Notebook
- Exhibit 13 - Pages from Common Laboratory Notebook

alternative lower alkyl acetates to have been readily apparent and obvious. Thus the instructions reflected in the common notebook disclosed or at least made obvious to one of ordinary skill in the art every aspect of claims 1-3 of U.S. Patent No. 6,476,220 B2.

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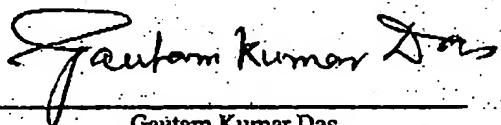
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